Medical Library
APR 11 1921

Volume V March, 1921 *Number 2*

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

Single Copies, $1.25
$6.00 Per Year

Published bi-monthly by
The Association *for the* Study *of* Internal Secretions
1100-1103 Title Insurance Building
Los Angeles, California

For
TISSUE ABSORPTION

Clinically Tested Solutions

In Hermetically Sealed Ampules
Sterile and Ready to Use

Each measured cubic centimeter contains the water-soluble extractive of two decigrams of the selected dried substance.

Dose, by deep intramuscular injection, one cubic centimeter. There is sufficient fluid in each ampule to permit the withdrawal of a full measured cubic centimeter.

List of Solutions

LUTEIN—CORPUS LUTEUM
OVARIAN RESIDUE
OVARY—WHOLE

In Boxes of 6 Ampules Each

Further Information Upon Request

Hynson, Westcott & Dunning
Baltimore

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

March, 1921

DIABETES INSIPIDUS AS A HYPOPITUITARY SYNDROME

G. MARAÑÓN, M.D.

Professor of the General Hospital of Madrid, Auxiliary Professor of the Faculty of Medicine.

In a recent book (1920) I have presented my clinical and experimental experience on diabetes insipidus. Data more recently acquired induce me to publish in this review the results of later observations on this problem, which in recent years has become one of much interest to pathologists.

The careful study, from the endocrine point of view, of 32 cases of diabetes insipidus collected during the last few years, has convinced me that this syndrome is, at least in a large majority of cases, a consequence of an insufficiency of the posterior lobe of the hypophysis. All clinicians, practically without exception, are agreed to this interpretation of the problem. On the other hand, among the physiologists there are a certain number of investigators who will not admit the hypophyseal pathogeny of diabetes insipidus: Among these are Camus, Roussy, Houssay, Leschke and others. But that is due, in my opinion, to the fact that they have not given to the clinical and anatomical-pathological data the biological value which they really possess, and which is often considerably superior even to that of physiological experimentation. When, after the studies of Fröhlich, of Lannois and others, the idea appeared in medicine that the origin of obesity lay in the hypophysis, there also appeared discussions which were almost identical with those which the problem of diabetes insipidus now presents. The difference between the data

obtained in the clinic and by experimentation were also noted; then the physiologists invoked the existence of a nervous centre at the base of the brain, which was said to be responsible for obesity; and they said, as now, that in cases of hypophyseal lesions accompanied by obesity, the latter depended on the indirect lesion of the nervous centre on account of the production of a tumor of the hypophysis, and not on the insufficiency of the secretion of this gland. At last, an agreement was reached and today the hypopituitary origin of obesity is a fact as solidly established as is that of the thyroid origin of myxedema (Marañón, 1920, b.)

The clinical argument is decisively in favor of the hypopituitary theory since in the great majority of cases of diabetes insipidus, clinical examination shows the existence of symptoms of hypophyseal lesions. And the analysis of the symptoms nearly always shows us an insufficiency in the functioning of the posterior lobe* of the gland, either primary or secondary to lesions of the anterior lobe. Our 32 cases† have given us the following results, from the endocrine point of view:

I. A boy of 15 years of age. Fröhlich's dystrophia adiposogenitalis. Normal sella turcica. Voids 5 liters of urine per day, which is very dilute and without abnormal substances.

II. A boy of 13 years of age. Fröhlich's dystrophia adiposogenitalis. Normal but rather deep sella turcica. Voids from 6 to 7 liters of urine per day.

III. A boy of 14 years. Fröhlich's dystrophia adiposo-genitalis syndrome and exceptionally low stature. Clinical symptoms of a hypophyseal tumor, which is confirmed by the radiograph. Urinates from 12 to 14 liters per day.

IV. A girl of 19 years, with normal menstruation, vitiligo, marked abdominal adiposity, normal sella turcica. Urinates 4 liters per day.

V. A girl of 26 years. Low stature, great abdominal adiposity, somnolence. The radiographic image shows a very small sella turcica, the anterior clinoid processes appearing in contact with the posterior. Urine, 6 liters per day, which is dilute and without abnormal substances.

VI. A boy of 19 years. Very neurotic; marked cachexia, without any lesion which would account for it. Small, elongated sella turcica, accompanied by polyuria of 7 to 8 liters per day. He died in cachexia, and we were unable to perform an autopsy.§

*When speaking of *posterior lobe*, we always refer also to the so-called pars intermedia, the functional separation of which from the posterior lobe seems to us to be, for the moment, arbitrary.

†In our book mentioned above (1) the clinical history, with photographs and radiographs of 24 of the cases, is presented in detail.

§In all of these cases, for the sake of brevity, we do not give details of the analyses of the urine, but it is understood that in all of them there were the usual characteristics of diabetes insipidus, e.g., low density, dilution of the normal constituents, absence of abnormal constituents, etc.

VII. A boy of 22 years. Very neurotic. Leanness of the cachexia type, voids 3 liters per day. Thirst, etc. Without symptoms of hypophyseal tumor. Radiograph of the head not taken.

VIII. A man of 50 years. Suddenly complains of marked asthenia, impotentia coiundi absoluta, became very thin without any apparent reason (tuberculosis, hyperthyroidism, neurathenia, cancer, etc., absent), thirst and polyuria of 3 and a half or 4 liters per day. Radiograph of the sella turcica normal.

IX. A girl of 15 years. At the age of 9 years she was greatly frightened and began to urinate from that time onwards from 9 to 10 liters per day. Stature almost dwarfish; infantilism, has not menstruated; sella turcica indistinct, giving the impression of an enlarged hypophysis.

X. A boy of 16 years. General and genital infantilism clearly marked. The radiograph showed a slightly but certainly increased sella turcica. Polyuria of 3 to 5 liters per day, thirst, etc.

XI. A boy of 15 years. From the age of 6 years, his growth has been retarded, and he now manifests a very accentuated type of infantilism and dwarfism. Urinates 8 to 10 liters per day, great thirst, etc.

XII. A girl of 15 years. From the age of 5 years she has been backward in growth; at the moment her stature is small with excessive adiposity which reminds one of Fröhlich's syndrome. Normal menstruation since 12 years of age. Silhouette of the sella turcica showed enlargement. Slight goitre and symptoms of thyroid insufficiency. Urinates from 9 to 10 liters per day.

XIII. A woman of 31 years. Shorter than all her brothers and sisters and very stout (Fröhlich's type). Very irregular menstruation, which does not appear for many months at a time. Urinates from 8 to 10 liters per day.

XIV. A boy of 13 years. Eunuchoid type, very long legs, cryptorchidic, etc., severe headaches with vomiting attacks. Urinates 7 to 8 liters per day.

XV. A man of 32 years. His aspect is that of a man of 50 years or more, his teeth have fallen out, hair becoming grey, wrinkles on his face, etc., atrophied genitalia and absence of the secondary sexual characteristics. Urinates 5 to 6 liters per day, has great thirst, etc.

XVI. A boy of 13 years. Shot in the cranium, and in consequence has been developing a typical adiposo-genital syndrome with a polyuria of 9 to 11 liters per day. The radiograph, surgical intervention and autopsy confirmed the existence of the shot at the extremity of the third ventricle, dividing the tuber cinereum.

XVII. A boy of 16 years. Marked traumatism in the head, serious concussion of the brain, and appearance of an intense polyuria which attains 18 liters per day.

XVIII. A man of 40 years. Marked cerebral traumatism with serious concussion. Since then polyuria of 14 to 16 liters per day has appeared and a tendency to adiposity and giddiness.

XIX. A man of 37 years, with acromegalic habitus since puberty, and considerable tendency to urinate, but within normal limits. Twenty years before he had contracted syphilis, which had been badly treated. Three years ago he developed a gumma in his leg and soon afterwards thirst and polyuria of 7 to 8 liters per day appeared, both of which ailments began to disappear with the anti-syphilitic treatment. Sella turcica plainly increased in size.

XX. A woman of 39 years. At 29 years of age, she was seriously eclamptic after giving birth to a child and since then a rapid in-

crease in weight, thirst and polyuria of 9 liters daily appeared, which has disappeared spontaneously in 5 or 6 months. At present she has glycosuria.

XXI. A man of 54 years. He was always much taller than his brothers, with very large feet and hands and mandibular prognatism. During the last year he had worried a great deal and since then had suffered from neurasthenia, a tendency to grow fat, thirst and polyuria of 4 to 5 liters per day.

XXII. A woman of 27 years. All her brothers are very tall, but she is taller than any of them. She has a marked development of the lower jaw. Her menstruation is always scanty and she has a tendency to fatness, especially of the abdomen and the hips. From the age of puberty to 18 years, she suffered from a polyuria of 5 to 7 liters daily which desisted spontaneously.

XXIII. A woman of 39 years. Much taller than all her brothers and than her parents. Menstruation always scanty; sterile; tendency to great fatness. From the age of 11 to 16 years she suffered from diabetes insipidus (6 to 7 liters of urine were voided per day). Quite nervous. Cured spontaneously.

XXIV. Woman of 28 years. Had a very intense Graves' disease for many years. Her father manifested a typical case of gigantism with acromegaly. She has slight mandibular prognatism, intense headaches, an enlarged sella turcica and very scanty menstruation. In spite of the hyperthyroidism, there is a tendency to put on fat. Great thirst and diabetes insipidus (4 to 5 liters) during the past three years.

XXV. A woman of 33 years, with a normal constitution and without any apparent symptom of an endocrine nature. Since she was a child she has suffered from diabetes insipidus (6 to 8 liters of urine daily). When we thought the examination from an endocrine point of view to be negative, we found on examining the abdomen that the whole anterior wall was covered completely with a thick hairy down, which she had not wished to show us. Besides this, she has a very scanty menstruation. Her voice becomes thick at times, and the face has become puffy in appearance in later years.

XXVI. A man of 32 years. Ten years ago, after an intense emotion and great physical fatigue, he suffered from polyuria which reached 15 to 20 liters. Great development of the frontal sinus, giddiness, sudden loss of sight; diminishing of the sexual libido and increase of epigastric adiposity. His attention was attracted by a considerable increase of hairy down on the abdomen, from the pubis to the umbilicus.

XXVII. A boy of 19 years. Diabetes insipidus (4 to 7 liters of urine daily) for the last 5 years. Little development of the genitalia, with absence of hairy down on the whole body save the abdomen, which had an abundance.

XXVIII. A woman of 31 years. Cancer of the breast with a great number of metastases in different organs. Headaches and polyuria of 5 to 6 liters per day during the latter months of her life.

XXIX. A man of 64 years. Cancer of the stomach in the last two months of his life, headaches, tendency to sleep, rapid loss of weight (in spite of the fact that he ate enough and did not suffer from digestive complaints); accompanying this he had a marked polyuria of 8 to 9 liters daily.

XXX. A woman of 45 years. Accompanying a large number of circulatory and nervous disturbances of the climacteric type and the disappearance of the menstruation, she suffers from great thirst and

polyuria of 4 to 6 liters per day. A great tendency to lay on adipose tissue.

XXXI. A woman of 48 years. A year ago she went through the menopause accompanied by a strong hyperthyroidic reaction, and since then has had diabetes insipidus (6 to 7 liters of urine daily) with great thirst, etc.

XXXII. A man of 38 years with moderate diabetes insipidus (3 to 5 liters daily); very intense thirst. He presents no morphological or functional symptom which can be related to the alterations of the endocrine glands, or symptoms of hypophyseal tumor. Ten years before he had had syphilis which was badly treated, and latterly had had an attack of purpura.

As can be seen, almost all these cases confirm the hypofunctional theory of diabetes insipidus. In cases I, II and III, it is a question of the typical Fröhlich adiposo-genital syndrome, now definitely considered as the clinical expression of the hypofunction of the posterior lobe of the hypophysis. In cases IV and V, this adiposity was limited to the abdomen, which, as we have seen, often occurs in lesions of the hypophysis, and in these cases it is confirmed by the disappearance of the adiposity, simultaneously with the polyuria, under hypophyseal opotherapy.

Cases VI, VII and VIII are typical of the hypophyseal cachexia, well known since the studies of Cushing, Pende, Simmond, Luzzato, Marañon (1920, b.), and others. The frequency with which one reads in old clinical histories of progressive cachexia in diabetes insipidus, is easily explained by the common origin of both processes (cachexia and polyuria) and not, as was formerly believed, because the excessive loss of water determined the loss of weight. Considering the frequency with which hypophyseal metastases are produced in cancers of the breast and certain abdominal cancers, it is possible that the cachexia of cancer is hastened in some cases (as in our observation XXIX, by a marked insufficiency of the posterior lobe of the hypophysis.

Cases IX, X, XI, XII and XIII, are either examples of pure dwarfism or are cases of dwarfism combined with infantilism and sometimes with adiposity of Fröhlich's type. At present the hypophyseal origin of dwarfism and the participation of the hypophysis in the polyglandular disturbance which causes infantilism, is admitted by all. It is certain that the anterior lobe of the gland appears in both cases to be directly responsible for the disturbance in growth, but it is easily understandable that the atrophic or sclerotic process, which has a tendency to invade

several endocrine glands, also invades the posterior lobe, united to the anterior lobe without solution of continuity, and then the polyuria, the adiposity, etc., appear.

In case XIV it was a question of an isolated example of genital insufficiency, with eunuchoid morphology and without a known etiology. Tandler and Grosz and other authors have shown clinically the participation of the hypophysis in these states of genital insufficiency, which are apparently primary. It is in fact very possible that in many of them a hypophyseal insufficiency exists which gives rise to the genital disturbance; and this case, with its symptoms of hypophyseal tumor (headaches and attacks of vomiting) would confirm it. Unfortunately the radiograph of the head did not come out well, and the patient went away so that it was impossible to repeat it.*

Case XV belongs to the syndrome called "insuffisanse pluriglandulaire" by the French authors, "gerodermia genitodistrofica" by Rumo and Ferranini and other Italian authors, and "Multipleblutdrüssensklerose" by the Germans. It is probably, as a matter of fact, a sclerotic condition which affects the whole endocrine system, comparable to that which physiologically appears in old age and, like this, is responsible for the aspect of senility of the patient. According to Lereboullet, syphilis is often the origin of this sclerosis. When the lesion affects the posterior lobe of the hypophysis, polyuria will result, as it resulted in the cases of Lereboullet and in ours. In this patient, we observed another phenomenon, which was also probably of hypopituitary origin: Slight attacks of intestinal paralysis with considerable meteorism, which rapidly yielded to pituitrin.

Case XVI has the value of a laboratory experiment, as the shot penetrated between the two cerebral hemispheres without producing the least nervous disturbance in the patient and settled in the parahypophyseal region, causing the adiposo-genital syndrome and diabetes insipidus. The fact that the shot did not wound the hypophysis itself, but the extremity of the middle ventricle, could be interpreted to their advantage by the partisans of the nervous theory of diabetes insipidus. But the histological examination of the gland showed that with section of

*In other cases of genital insufficiency of the eunuch type (without polyuria) that we have observed, we have obtained good results on the genital development with hypophyseal opotherapy; and in one case with the grafting of two hypophyses of sheep into the tibia.

the pituitary stem occurred cicatrization, which invaded the posterior lobe of the hypophysis. In addition, apart from the polyuria, there were in this case adiposo-genital changes which undoubtedly depended on the endocrine insufficiency of the hypophysis. In cases XVII and XVIII, we suppose that the traumatism produced a hemorrhage of the posterior lobe of the hypophysis, which caused the transitory insufficiency, expressed by diabetes insipidus. In post-mortem examinations of persons dead through traumatisms of the head, falls, collisions, etc., we have been able to confirm, in the Judicial Deposit of Madrid, the ease with which these hypophyseal hemorrhages can be produced. In case XVIII the tendency to obesity confirmed the diagnosis of the hypophyseal lesion. In both cases the admirable result of the injection of pituitrin pointed also to this etiology.

Case XIX was, from birth, an example of attenuated acromegaly. Probably this abnormal state of the hypophysis favored the fixation or stay of the syphilitic organism. Moreover, Bernario has shown the frequency with which gummas of the neurohypophysis give rise to the diabetic syndrome.

In case XX, the puerperal infection probably attacked the hypophysis, as is proved by the polyuria coinciding with the rapid increase in weight. According to Massalongo and Piazza post-infectious obesities are almost always of hypophyseal origin* and Motzfeldt attributes to the hypophyseal insufficiency, not only the cases of post-infectious diabetes insipidus published recently, but also even the transitory polyurias which are frequently observed after infections.

Cases XXI, XXII and XXIII are very similar. All three are examples of hyper-hypophyseal constitution, actual attenuated acromegalies, as in case XIX. One can suppose that in them the hypertrophy of the anterior lobe, characteristic of acromegaly, compressed the posterior lobe within the sella turcica, and provoked the polyuria. Creutzfeld and Pittaluga also give this explanation for their cases of acromegaly with polyuria. Sometimes other symptoms of insufficiency of the posterior lobe accompany the polyuria, such as obesity and genital insufficiency

*One of our recent cases which will shortly appear in the Revue Neurologique, of Paris, showed that the hypophysis not always intervenes in these cases, although it may appear to do so clinically.

(Case XXIII). This compression of the posterior lobe may be transitory, as probably occurs in these predisposed cases, during the pubescent reaction of the anterior lobe, which is responsible for the rapid growth which many youths undergo during this period. This would be the explanation of many cases of diabetes insipidus of the pubertal period, which are cured spontaneously (XXII and XXIII). In the case of observation XXIV, this same mechanism can be invoked to explain the polyuria: hypertrophy of the anterior lobe, large sella turcica, physiognomical acromegalic features, inherited from a father, and compression of the posterior lobe (polyuria, adiposity and scanty menstruation).

Cases XXVI and XXVII are very interesting, as, in them the hypophyseal change is manifested almost exclusively by the symptom of increased hairy down on the abdomen, almost monstrous in case XXV, and less intense, but also very marked in cases XXVI and XXVII. This symptom of the acromegaly, quoted by various authors—Falta, Barker and Hodge, and others, was found by us in almost all the cases of that illness, and we do not know if it is due directly to the hypersecretion of the anterior lobe of the hypophysis or, as Falta believes, to a hyperfunctional reaction of the cortex of the adrenal glands which frequently accompanies acromegalic conditions. The fact is that its presence allows us to suspect strongly the existence of a change in the anterior lobe of the hypophysis, of which there were evident symptoms in cases XXV and XXVI. The insufficiency of the posterior lobe (polyuria) is explained by the mechanism noted above.

Cases XXVIII and XXIX are probably instances of cancerous metastases in the hypophysis. Simmond and Sekiguchi have shown the frequency with which polyurias appear, as in my case XXVIII, in the course of cancer in the breast, without other symptoms of hypophyseal lesion; and the post-mortem examination showed that it was a question of a small metastasis in the posterior lobe. Arnstein has described a similar case in a cancer of the digestive apparatus, resembling our case XXIX.

Cases XXX and XXXI are instances of diabetes insipidus appearing in the course of the climacterium. We have shown (1919) the frequency with which one can find manifestations of hypophyseal insufficiency at the climacterium, which are respon-

sible for many of the disturbances which women usually suffer at this period of life.* Among these disturbances diabetes insipidus may be reckoned, since it occurred in these cases. In case XXX the polyuria coincided with a sudden tendency to adiposity; in case XXXI there were no other hypophyseal symptoms, but there was a strong reaction of the thyroid. Case XXXI, which could be considered as one of climacterium virile, could be added, in a certain way, to the former cases.

There remains only case XXXII, of all those collected by us, which does not present direct or indirect symptoms permitting us to suspect a hypophyseal lesion. As we saw the patient only once, we were unable to examine the condition of the sella turcica and determine if anti-syphilitic treatment would diminish the polyuria (which would have allowed us to correlate this with case XIX).

In any case *our clinical experience overwhelmingly demonstrates that diabetes insipidus is, almost without exception, connected with a disturbance of the hypophysis; and more exactly, to a disturbance of the posterior lobe of the hypofunctional type.* It is very important to note that the majority of our cases (and the same thing occurs with those published by other authors) *are absolutely opposed to the hypothesis that it is a matter of tumors of the gland which, by secondary pressure on the neighboring nervous centres, and not by an endocrine disturbance, produce the polyuria;* since in nearly all cases the *lesions were not tumors* but were sclerosis, atrophy, hemorrhage, etc., as was proved by the clinical and radiographic examination.

Great value is also attached in this regard to the favorable result of hypophyseal opotherapy. I do not understand how one can doubt the biological significance of the fact that the injection of the extract of the *organ which the clinical and post-mortem examination shows to be diseased in diabetes insipidus,* is *the only therapeutic means,* among so many which have been used through the ages, which in a *certain and safe manner* suppresses the polyuria. One cannot suppose that it is a question of a general action of these extracts, as *other polyurias, such as that of chronic nephritis* or *that of diabetes mellitus, are not influenced*

*This interpretation contradicts that of Culbertson in which many of the symptoms of the menopause are attributed to hyperfunctioning of the hypophysis. This point of view has been discussed at length in our book.

by pituitrin, or are influenced to a very slight degree, as we have proved repeatedly. In consequence of the combined evidence of the curing of the polyuria of diabetes insipidus and not the other polyurias; and the efficacy of the extract being precisely that of the gland which is found to have a lesion in this disease and no other extract or inorganic substance whatever having a like effect —I think one can assert, with Hoppe-Seyler, that the curative action of pituitrin in diabetes insipidus has the same value as that of thyroidin in myxedema; that is to say, that, even in the absence of other clinical symptoms, it is sufficient that the polyura diminishes or disappears after the injection of the drug for one to decide upon the hypophyseal origin of the disease.

Of our 32 cases the therapeutic test was made in 19 (observations I, III, IV, V, VI, VIII, IX, X, XII, XIII, XIV, XV, XVI,, XVII, XIX, XXI, XXIV, XXV, and XXVI), and in all but two cases it was positive; moreover these can be eliminated as cases of negative tenor, since they were precisely two patients who certainly had hypophyseal disturbances (Observation I: dystrophia adiposo-genitalis; and XXIV, Graves' disease and slight acromegaly, with a large sella turcica, in a daughter of an acromegalic giant.) In order to judge with exactitude the inefficiency of pituitrin, it would have been necessary to repeat several times the proof with other samples of the medicament, because, as Hartman has pointed out, not all extracts have the same composition, and they are sometimes decomposed. As a matter of fact, in case V we obtained no diminishing of the polyuria with the first injection; but one month afterwards a fresh injection lowered the quantity of urine from 5 to 3 liters in 24 hours. In case XXVI, the first injection with old pituitrin diminished the 10 liters which were originally voided daily by only 1 or 2 liters; while fresh pituitrin diminished it by 6 liters per day.

A very interesting fact, to which some authors have called attention, but which I think has not been sufficiently emphasized, is that pituitrin, used in the same dose for different cases, (0.5 or 1 cc. of the commercial solution) produces in various patients a different effect, inversely proportional to the intensity of the polyuria.* That is to say that in patients with great polyuria, the effect is greater than in those with less polyuria; and in

*Recently F. Brun has insisted on this fact in a work which we have read whilst writing the present article.

both the former and the latter, whatever the dose given, the quantity of urine is never less approximately than normal. For example, 1 cc. of pituitrin lowered the quantity of urine in case III, from 12,000 cc. to 1,900 cc.; in cases XII and XIII, from 9,000 cc. to 2,000 cc.; in case XVI from 9,600 cc. to 1,300 cc., while in observation IV, the diminution was only from 3,500 cc. to 1,600 cc.; in observation VIII, from 4,000 cc. to 1,700 cc.; in XXI from 4,100 cc. to 2,000 cc. In no case was the reduction less than 1,500 cc. It appears then, *that pituitrin is only able to act on pathological polyuria, by reducing it to normal, but without reducing it below this limit.* This effect is obtained almost equally with a dose of 0.5 cc. as with 1 cc. of the commercial pituitrin. *Doses greater than* 1 *cc. do not increase the oliguric capacity of the drug.* As a confirmation of these points of view, we have observed that in normal man and animals, the injection of pituitrin acts very slightly, or not at all on the quantity of urine; but if we take a polyuric rabbit, and make it imbibe an excessive quantity of water (Motzfeldt) or inject it with physiological salt solution (Marañon and Rosique), we then observe clearly that the urine output falls to the normal values. An increase in the quantity of pituitrin injected in the rabbit is not followed, as is true also in cases of diabetes insipidus, by a proportional diminution in the quantity of urine; only when the dose is very excessive and frequently repeated, do *oliguric* phenomena induced by acute nephritis occur. In such cases are noted albuminuria and marked lesions of the kidney, as I have demonstrated with Pascual.

For all these reasons, we think that the internal secretion of the posterior lobe of the hypophysis exercises, physiologically, a controlling action on the elimination of water through the renal filter and that, through the disturbance of this controlling mechanism, diabetes insipidus is produced. We cannot discuss here what this mechanism may be (see Marañon, 1920, a), but we will say that, in our opinion, the hypophyseal *oliguric* hormone may perhaps act, partly directly on the renal cell (either increasing its power to concentrate dissolved matter, or increasing its capacity to retain water), and partly by means of the nervous system, collaborating with the *oliguric* centers at the

base of the encephalon as postulated by Pende. The modifications of these centers would be transmitted to the kidney, probably by way of the sympathetic, as some of our experiments and especially those of Motzfeldt seem to show.

It is very probable, as Cushing and Biedl have suggested, that the hypophyseal hormone ascends by the tuber cinereum to act on the proximal mesencephalic centers. Our observation, XVI, which we have presented in detail elsewhere (Marañon and Rosique, 1917) is, in this sense, very important, as the lesion producing a very intense diabetes insipidus was, as the histological examination confirmed, the fibrous scar which was produced around the shot which separated the hypophysis from the nervous tissue of the infundibular region.

The role of the cerebrospinal fluid in this mechanism is not made clear by our experiments. Some authors suppose that the internal secretion of the hypophysis passes to and is diffused in it. But we have shown (Marañon and Gutsinger, 1919) that the *cerebrospinal fluid does not possess the the slightest oliguric action,* either in cases of normal individuals, nor in those of diabetes insipidus patients. Moreover, according to this hyphothesis, the injection of pituitrin directly into the spinal canal should be much more efficacious than when injected intravenously; but in four of our observations on diabetes insipidus (XIV, XVII, XXV, and XXVII) we injected pituitrin (0.5 cc. and 1 cc.) into the spinal canal *without obtaining a greater diminution than when intraveneous injections were made.*

However, *hypertension of the cerebrospinal fluid is a constant phenomenon in diabetes insipidus, and the extraction of a certain quantity of the fluid diminishes the polyuria,* as is shown by the cases of Graham, Williams, Motzfeldt, Costagli and three of our four patients on whom the experiment was made (observations XIV, XVII, XXVII). In observation XIII, on the other hand, the diminution was insignificant (150 cc.). It is difficult to explain this phenomenon, except by supposing that the hypertension, distending the base of the middle ventricle, opposes the supposed ascent of the hypophyseal hormone from the gland, through the pituitary stem. As to the origin of the hyper-

tension, it is difficult to fix it in cases where there are no hypophyseal tumors, as occurred in some of our cases.*

Finally, I wish to insist on the importance, according to my experience, of the emotions in the pathogeny of this disease. Lereboullet, Van der Heijden and Germani all report an initial terror in the clinical history of their polyuric patients. In several of our observations the origin of the polyuria also coincided with an emotional state which was either brusque (fall in cold water in observation IX, as in the cases of Van der Heijden and Lereboullet, serious quarrels with parents as in observation XXVI), or slow and depressing (a period of great intellectual effort and fear of an examination, as in observation VI; serious matrimonial troubles which led to divorce as in observation XXI). Besides, in all the cases, the polyuria increased considerably during emotional states. It is obvious that in these cases there was an easily demonstrable predisposing factor (infantilism, obesity, IX; great development of the sinus frontalis, giddiness and sudden loss of sight, epigastric adiposity and abdominal down in observation XXVI; abnormal smallness of the sella turcica in observation XXVII; great height and acromegalic characteristics in observation XXI). But the fact is interesting, when bearing in mind the role which the internal secretions certainly play in the mechanism of the emotions. One of the proofs of the intervention of the endocrine system in the development of the emotions, is precisely the frequency with which, in predisposed individuals, are produced certain diseases of the glands of internal secretion, due to the emotional states; for instance, Graves' disease, which is often a pathological prolongation of the vegetative modifications of the emotions (exophthalmus, tremor, perspiration, diarrhoea, tachycardia, palpitations, etc.). In the same way one can imagine that diabetes insipidus is related to emotional polyuria, which is transitory in individuals not predisposed.—September, 1920.

---

*Weed and Cushing admit a stimulating action of the internal secretion of the hypophysis on the choroid plexus. But this hypothesis cannot be applied to cases of diabetes insipidus in which there is a pituitary hyposecretion and, in consequence, a lesser stimulus.

BIBLIOGRAPHY

Arnstein, A.: Hypophysäire Polydipsie. Wien. klin. Wchnschr., 1919, **32**, 928.

Barker, L. F., & Hodge, Mary: On the control of diabetes insipidus by means of hypophyseal extract in multi-glandular endocrinopathy (thyreo-hypophyseo-genital syndrome). Endocrinol. (Los Angeles), 1917, **1**, 427-432.

Benario, J.: Zur Pathologie und Therapie des Diabetes insipidus. München. med. Wchnschr., 1919, **60**, 1768-1771.

Biedl, Artur: Innere Sekretion, etc., 2te. Aufl., Berlin, 1913.

Camus, J., & Roussey, G.: Diabète insipide et polyurie hypophysaire; régulation de la teneur en eau de l'organisme. Presse méd. (Par.), 1914, **22**, 517-521.

Cannon, W. B.: Bodily changes in pain, hunger, fear and rage. N. Y., 1915.

Costagli: Il diabete insipido e la sua origine ipofisaria. Riv. crit. di clin. med. (Firenze), 1919, **20**, 571.

Crile, G. W.: The origin and nature of the emotions. Phila., 1915.

Culbertson, C.: A study of the menopause with special reference to its vaso-motor disturbances. Surg., Gynec. & Obst. (Chicago), 1916, **23**, 667-685.

Cushing, H.: The pituitary body and its disorders. Boston, 1912.

Falta, Wilhelm: Die Erkrankungen der Bluturüsen. Berlin, 1913, J. Springer, 562 p., 1 pl. 4°.

Germani, A.: Intorno ad un caso di diabete insipido. Morgagni (Milano), 1917, **59**, 165-177.

Graham, E. A.: Diabetes insipidus as a sequel to a gun-shot wound of the head. Ann. Surg. (Phila.), 1917, **66**, 529-531.

Hartman, F. A.: Hormone control of renal function. Endocrinol. (Los Angeles), 1918, **2**, 447-451.

Hoppe-Seyler, G.: Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt. München. med. Wchnschr., 1915, **62**, 1633-1635; 1916, **63**, 47.

Houssay, B. A.: The pituitary body and polyuria. Endocrinol. (Los Angeles), 1918, **2**, 94-97.

Leschke: Diabetes insipidus, seine Beziehung zu der Hypophyse und dem Zwischenhirn. Ztschr. f. klin. Med. (Berl.), 1917, **87**, 201.

Luzzato: Cited by Y. in Riv. crit. di clin. med. (Firenze), 1918, **19**, 91-92.

Marañón, G.: Le édad critica. Madrid, 1919, 501 p. Sociedad Española de Publicaciones Médicas, Madrid.

——: (a) Nuevas Orientaciones sobre la Diabetes Insipida. Madrid, 1920.

——: (b) Las enfermedades de la nutricion y las glandulas de secrecion interna. 3rd ed., Madrid, 1920.

Marañón, G., & Pintos, G.: Lesion traumatique pure de l'hypophse. Syndrome adiposo-genital et diabète insipide. Nuov. Icon. de la Salpêt. (Paris), 1910, **28**, 125.

Marañón, G., & Rosique, A.: Contribucion clinica y experimental al estudio de la hypofisis sobre la diuresis. Treb. de la Soc. d. biol. d. Barcelona, 1917, **17**, 126.

Massalongo, R., & Piazza, P.: Sindrome ipofisiaria adiposo-genitale post-infettiva. Riforma med. (Napoli), 1914, **30**, 1048-1077.

Motzfeldt, K.: Experimental studies on the relation of the pituitary body to renal function. J. Exper. Med. (N. Y.), 1917, **25**, 153-188.

——: Diabetes insipidus. Endocrinol. (Los Angeles), 1918, **2**, 112-121.

Pende, N.: Endocrinologia; patologia e clinica degli organi a secreziono interna. Milano, 1914, F. Vallardi. 802 p., 23 pl. 8°.

Sekiguchi, S.: Hypophyseal disorder in mammary cancer and its relation to diabetes insipidus. Ann. Surg. (Phila.), 1916, **63**, 297-304.

Simmonds, M.: Ueber sekundäre Geschwülste des Hirnanhangs und ihre Beziehung zum Diabetes insipidus. München. med. Wchnschr., 1914, **61**, 180.

——: Hypophysis und Diabetes insipidus. Ibid., 1913, **60**, 127.

Simmonds, M.: Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie. Deutsche med. Wchnschr. (Leipz. & Berl.), 1918, **44**, 852-854.

Tandler, J., & Grosz, S.: Die biologischen Grundlagen der sekundären Geschlechtscharaktere. Berlin, 1913, J. Springer, 56 p., 12°.

Weed, L. H., & Cushing, H.: Studies on the cerebro-spinal fluid. VII. The effect of pituitary extract upon its secretion. Am. J. Physiol (Baltimore), 1915, **36**, 77-103.

Williams, J. R.: Diabetes insipidus; study of the effect of pituitary administration. Endocrinol. (Los Angeles), 1917, **1**, 312-325.

HYPOPHYSIS TUMOURS IN DOMESTIC ANIMALS

DR. H. A. VERMEULEN,
UTRECHT, HOLLAND

After thyroidectomy, hypertrophy of the pituitary body, with obvious formation of colloid substance has been repeatedly described. In rabbits, Stieda found that nine weeks after the extirpation of the thyroid gland, the weight of the hypophysis had doubled. Also after castration, enlargement of this organ has been observed in man, the rabbit and in birds. Exceptions have, however, been reported. Hans Kühn came to the conclusion that castration is of no influence on the dimensions and the weight of the pituitary body in horses (Dissertation, Bern, 1910). Pathological enlargement of the hypophysis can take rise in three different ways: (1) originating from rests of the hypophysis vesicle, (2) originating from the ependyma of the infundibular canal, (3) by hyperplasia of the glandular part.

Rests of the hypophysis vesicle are often met with in quite normal hypophyses as small cysts, lined with epithelium. These occur regularly in ruminants, pigs and carnivores, but not in horses. When they can be demonstrated, they indicate the development of the glandular part as a vesicular body, isolated from the dorsal pharyngeal wall. Among the vertebrates, only in Ammocoetes, the larvae of Petromyzon, the direct communication between the hypophysis vesicle and the pharynx persists during life; in all other vertebrates it is fully isolated in a very early period of embryonic development and placed in the cranial cavity, before the basis cranii is closed. In several mammals a permanent cranio-pharyngeal canal has been seen, not seldom quite accidentally during a section, in cases in which no clinical symptoms had indicated its existence during life. In such instances the sphenoid is perforated and filled up with a continuation of the pharyngeal mucous membrane.

Originating from the epithelium of the hypophysis vesicles or rests of these in the glandular part of the organ, and from the epithelium of a canalis cranio-pharyngeous persistans, malignant tumours may destroy the pituitary body. A striking example of this manner of development of hypophysis tumours in

the horse has been described by Wolff (Dissertation, Bern, 1916). On the base of the brain of a horse of six years, Wolff found a tumour weighing 80 grams (the normal weight of the hypophysis of a horse is about 2½ grams.) This tumour had extended through a slit in the sphenoid into the sphenoidal sinus, which was fully filled up with the tumour tissue.

In our domestic animals the infundibular canal extends into the nervous part of the pituitary body in a variable way. In the horse, no extension of this canal is to be found; in ruminants we can trace a small continuation of the canal in the pars nervosa; in pigs this continuation is more distinct, but in carnivores the infundibular canal may extend throughout the length of the nervous part. Malignant tumours can also take origin in the epen dyma of this canal. Of this way of development of hypophysis tumours, too, examples are known in the veterinary pathology. In the "Bulletin Centrale de Mèdicine vétérinaire," 1890, Mollereau describes a hypophyseal tumour in a horse 9 years old, which, microscopically was found to be only epithelium of the pars nervosa. It was gray in color, friable and the size of a hazelnut. It lay quite centrally. In the horse, the nervous part of the pituitary body, incidentally, does not lie behind the glandular part, as is the case in man, but is wholly surrounded by the glandular part, so that it is to be seen only in cross section.

In his dissertation (Bern, 1911) Valenta describes a hypophyeal tumour in a cow. This neoplasm weighing 62 grams had caused an enormous dilatation of the sella turcica and had also grown out from the centre.

Hyperplasia of the glandular part has been seen by myself in two horses and in a goat. In a mare of 8 years I found a large, hard hypophysis tumour of the shape and the size of a small hen's egg, weighing 36.6 grams. The tumour lay in a pit in the base of the brain at a depth of 1.8 centimetres. The corpus mammillare, the medial parts of the pedunculi cerebri and the corpus cinereum were totally destroyed. On cross section a strong fibrous capsule and, on the cerebral side, large hemorrhages were found. This tumour was constructed wholly of eosinophil cells in which fine and thick bundles of connective tissue and cysts, more or less filled with a colloid substance, could be observed. A second case of eosinophile hypophysis tumour I saw in an old horse. It was round in shape and the size of a

hazel-nut. Remains of old hemorrhages were also in this case to be seen on the cerebral aspect.

Attention may be drawn to the remarkable fact that, in the case which Wolff described and in the first case observed by myself, the clinical symptoms were characterized by a high degree of somnolence, which under the same circumstances is also observed in man.

In a hermaphroditic goat that during life, had not shown any symptom whatever of cerebral disease, I found a large hypophysis, which reached the pons cerebri; it had five times the weight of the normal organ. In the pars intermedia, enormous colloid cysts occurred, and also, but in a minor degree, in the markedly hyperplastic glandular part.

I regret that I had no occasion to examine the thyroid gland of this animal.

PHYSIOLOGICAL HYPERTHYROIDISM*

HARLOW BROOKS

NEW YORK CITY

Physicians everywhere are now intensely interested in every sort of disease and disturbance of the ductless glands. Probably no other one subject is just at this time receiving so much attention. As a result of this, a better understanding of the disturbances of the ductless glands is becoming very widespread, both in the profession, and unfortunately, perhaps, also, among the laity. As the result of this last, encouraged largely by the now popular pseudo-medical reports in the general magazines and the public press, the practitioner is frequently brought into contact with cases in which this small sum of knowledge is working out quite other than beneficially for those so instructed. Some of the medical profession also are becoming obsessed with the idea that these interesting structures are concerned only with the production of disease and that they exist but for the purpose of causing work for the physician and surgeon.

In this short paper it is my aim chiefly to point out a condition under which symptoms of thyroid disturbance appear, symptoms mistakenly regarded as indicating serious and permanent disease. The interesting fact, of course, to be deduced from these cases, is that treatment should not be directed to prevent or circumvent these efforts on the part of the gland, but that, while in many instances it may be necessary to direct or guide nature's efforts, it is unwise to attempt measures, and particularly radical measures, which inflict changes or limitations of a permanent character on the gland in question.

Doubtless there is no more familiar example of physiological hyperthyroidism than is frequently seen in the developing youth. In fact, many of the characteristics which we regard as a part of youth itself are but probable evidences of thyroid activity.

The full necked youth is so because of the prominence which the thyroid begins to assume at about this age, and a study of

*Read before the Williamsburg Medical Society, Brooklyn, January 10th, 1921.

the work of the greatest artists, ancient and modern, illustrates this fact most graphically: note the young girls of Greuze and the wonderful singing boys of Donatello.

There are many conditions which, particularly in youth, are met only by an active secretion on the part of the thyroid; in fact, very many of the so-called youthful characteristics are really manifestations of thyroid activity. The alert, aggressive attitude of the healthy young man and the similar, though feminized, pose of the healthy young woman are in large part an evidence of thyroid activity. The tremor and blushes, the sentiment of the young woman, the nervous apprehension of the young man under emotional stimulation, are also largely, though not exclusively, evidences of thyroid activity. The blushing of the sensitive young girl or boy is but a neuro-circulatory reflex, exaggerated, through an over-activity of the thyroid, into the neuro-circulatory instability of the definitely hyperthyroid patient.

The tachycardia of the pronounced hyperthyroid patient is represented in the physiological hyperthyroidism stage by that condition of palpitation in which, in the words of the poet, "His heart went pitti-pat and hers went pity 'Zekial."

In the teens and early twenties new tissues are being builded with tremendous rapidity, particularly in the more complex mechanism of the female. Such being the case, the physiological demand for an increased thyroid secretion is often met by an increase in the size as well as in the activity of this gland, and in most instances this is induced by a hypertropy or hyperplasia, as well as by a mere hyper-secretion of the gland. The large and prominent thyroid is frequently, then, at this period of life and genesis, as typical a normal phase as the appearance of straggling hairs on the chin and upper lip of the youth, and the inclination of the mentality and emotional side of both boy and girl toward the development of sex characters and full maturity. The more charming the young woman, the more virile and attractive the youth, the more constantly will it be found that a large gland is present and the more certainly will it be noted that, under normal conditions, such a person responds to emotional and mental stimuli with a quick, aggressive and ap-

propriate reaction, which, after the manner with impetuous youth is frequently over-action.

Still another physiological evidence of thyroid activity or over-activity in the youth, and purposed doubtless by the great need at this period of growth and development, is an increased demand and utilization of food. The healthy and attractive young man and young woman at this period of life are possessed of good appetites, and the basal metabolism should be high at this period.

Again, at this time, artistic perceptions are most keen. In this so-called "formative period" of life, the young musician is most open to the development of his art and to the rapid acquisition of its technic; the young artist, actor or writer, particularly the young poet, is most capable of flights of imagination and of artistic conceptions, though, of course, the mature artist is better able to express and to elaborate his dreams. All these traits are dependent, at least to a considerable extent, upon a certain degree of thyroid flexibility and over-activity, and a study of the portraits of notable people at this period of their lives will commonly show that there is a large thyroid gland present.

It will also be found that in youth, and to a lesser but still perceptible extent among adults, periods of great emotional output, such as courtship, early months of marriage, and the more active phases of an artistic career, are accompanied by enlargements, though perhaps temporary, of the thyroid. The tremor, characteristic of both the hyperthyroid and the enthusiast, may be present, and even exophthalmus may become evident or accentuated.

This tendency is shown particularly in the pregnant young woman, in whom an increased emotionalism is quite likely to be present, especially in earlier pregnancies. In these there is also, according to many obstetricians, an increase in the demand for hypernourishment. An increase of thyroid activity is also necessary at this time because of the demands incident to the building of the new fetal tissue. Many of the activities of the body are noticeably exaggerated under these conditions in perfectly normal and normally reacting individuals. This fact is well illustrated in the madonnas of the great masters of painting. Besides

the enlargement of the thyroid gland there is also normally present in most pregnant women a quite definite enlargement of the fingers and hands, together with many alterations in the facial lineaments which perhaps the artist has been better able to recognize than has the physician. There is a certain beauty which appears in the face of the normal woman during and after her early pregnancies which causes pregnant or recently delivered women to be chosen invariably by great artists for their models of madonnas.

There is also, beyond doubt, something closely allied to a diminished action of the thyroid gland that renders the old maid less generous and self-sacrificing, less spiritually beautiful than the pregnant or parturient woman. That this trait is by no means a cultural one, is shown by the well recognized fact that the same spiritual and facial evolutions are also manifest in the highly bred horse or dog, and probably also in many of the other animals, even among the widely diversified and most savage of the cat family.

Very similar, though far less marked, and, of course, much less permanent alterations are noticeable in the thyroid during the menstrual periods. As a rule, and this has been observed by many intelligent lay women, the thyroid enlarges during the early days of the menstrual epoch, again showing the very close association which exists between the activities of the sexual functions and those of the thyroid. It is doubtless because of this that we find so consistently variations in the thyroid activity, and coincidentally in the thyroid bulk, in association with the sexual waves and doubtless for this, more than for any other reason, disturbances of the one gland are quite likely to be associated with abnormal reactions on the part of the other.

In many courtships, especially those of a highly dramatic or emotional type, thyroid enlargement takes place, even to a pathological degree. Under such circumstances the hyperactivity of the thyroid may become so manifest that marked neuro-vascular instability, exophthalmus, severe tremor and thyroid tumor of even a disfiguring degree may rapidly develop. When such a courtship terminates in a happy and normal marriage relation all these abnormal manifestations, as a rule, lessen or disappear.

A young woman of twenty years, who had been under my observation for some time, was brought to me with a definite picture of mild exophthalmic goiter which had developed during a period of not over two months. She had always been of an emotional type, was an excellent musician, fond of art, dancing, and sports of all kinds. Because of her beauty and charm she was very much sought after, and at times was considerably imprudent on account of her social desires and obligations. She had, however, remained a very healthy and active girl, due largely no doubt to her interest and skill in outdoor sports.

She had required very little medical attention and represented a very delightful example of attractive girlhood. She had never apparently been in love before, nor did she appear to have much conception of physiological love, preferring usually for her intimate associates her girl friends.

A chance meeting with a young army officer developed on both sides into a very rapid and fervent love affair. The young man's expected early order to active service abroad, with all the dramatic elements then stirring, profoundly affected the girl, and she rapidly developed a quite unmistakable case of hyperthyroidism of sufficient degree to be classed as early Graves' disease. She was then referred to me for advice as to the advisability of immediate operation, either the tying of the arteries or the probable removal of a segment of thyroid tissue.

Knowing the mother to be likewise of an intensely emotional type, and herself possessing a notably large thyroid, I advised that the patient be isolated from all outside influences, put to bed, and submitted to a long medical course of treatment before surgical treatment was resorted to. Little was accomplished during the two weeks this method was being enforced, although I believe that I had the thorough cooperation of the patient. At the end of this time, the sympathy of the mother and, I believe, her dramatic impulse which she has subsequently aptly and characteristically referred to as her "maternal comprehension," caused her to side with her daughter and an immediate marriage was consummated. My late patient then proceeded to her husband's station in company with him. The marriage proved happy and was shortly followed by an uneventful pregnancy, the delivery of a fine, healthy child, and the ap-

parently complete cure of the young mother, who is now more happy and content than ever.

Other instances of a similar character have occurred in my experience, though none has been quite so definite and pronounced in its effect. The lesson for me, I hope, has been a better understanding of the relationship between the emotionalism of youth and the effects of its thwarting on the thyroid gland, and also the effect of a perfectly normal and human outcome in the cure of this state.

My experience has been in no way different from that of any other physician, and I have, like many others, come to look for the cause behind hyperthyroidism, and when the condition has been of a physiological nature, have tried to act along physiological lines in the attempted cure, rather than to assume it a pathological condition demanding drastic or eliminative measures.

Very many cases of hyperthyroidism also appear to be due to too deep a drain on the emotionalism along mental rather than physiological or physical lines, as indicated in the case above cited. I have seen examples of this in temperamental young girls in their relation to school and studies, particularly in schools of music and art. I have observed, for instance, many examples of mild hyperthyroidism, occasionally approaching a Graves' picture, in a group of young women of a certain art center in which the conditions of life are very intense and highly competitive. Almost without exception, a withdrawal from competitions, an application of art to outdoor life or an arrangement so that sufficient rest and physical diversion are supplied, have sufficed to check or cure these cases without, at the same time, precluding a normal ambition and interest in life. I am told that a colleague has had a very similar experience among young actresses and singers.

Nor are such experiences limited solely to young women. There is rarely a graduating class at the medical college in which I have taught for the past twenty-five years that does not present one or more examples of similar conditions. As a rule, these manifestations do not appear in these young men before the third or fourth year of their studies, but it is quite unusual for the season to pass without several of them consulting me, either as physician or friend, because of hyperthyroid disturbances that

have usually been fully recognized as such by the students themselves. Palpitation of the heart, neurovascular instability, and over-excitability are the most frequent manifestations complained of; but in some, sweating when under nervous strain, inability to concentrate, insomnia and abnormal apprehensions are the striking symptoms. As a rule, on examination the young man displays a rapid and ofttimes irregular heart action which is checked or mitigated, to some degree at least, by moderate physical exercise and diminished by rest and sedatives, and also by psychic assurance, etc.

Many of these young men are made very miserable by these symptoms; some of them are brought to consent to operative or x-ray treatment of the thyroid, or consider giving up their studies, perhaps permanently. I myself was at first inclined to feel that many if not most of these young men were poorly fitted for the strain and rigor of a physician's life, but a broader experience has decided me against such a serious conclusion.

The young men who are most likely to develop these symptoms and signs of hyperthyroid activity are among the most desirable and brilliant of the students. Very frequently, however, they are men who, through over-ambition, poor antecedent education, poorly chosen nourishment, or insufficient rest and relaxation, have excited the condition by their habits of life and of study. I have noted the fact that many of these students suffered considerably from apprehension in regard to their studies and examinations and my experience has been such that I now have no worry about the results of examination in case of the boys who worry about them themselves, for they have always been among the highest in standing, not only in their examinations, but also in their professional after-life.

One such young man, I remember with especial vividness, because I now frequently see patients with him and have therefore become well acquainted with his success, and I feel also that I now understand the elements which led up to it. When he first came under my observation as a second year student he was twenty years of age. He came of poor, uneducated, but ambitious and intelligent parents, and during his entire course was obliged to support himself in large part by outside work. This resulted in insufficient rest, irregular and poor food, and con-

siderable strain. In addition, he was quite apprehensive as to his ability to pass his examinations, because of the unfair conditions under which he worked as compared with his fellow students. This anxiety was groundless, however, for he was recognized throughout his course as one of the most promising of the students, and while his conditions of life prohibited his sharing many of the pleasures of his fellows, he was one of the best liked and most popular men of his class.

The boy first came under my profesional care during his third year, and at this time was fully aware of his condition. He suffered extremely from attacks of tachycardia, associated with hot and cold flashes, profuse perspiration, tumultuous heart action, great nervous apprehension, a tremor which seriously interfered with his laboratory technic, and increasing insomnia. He was unable to eat sufficiently or properly and was losing weight rapidly.

Physically he presented marked enlargement of the thyroid, a considerable degree of exophthalmus, marked tremor, dermographia, and many other indications of unstable neurovascular control. His scholarship, however, still remained of a very high standard. The serious questions which presented themselves were: Was he able to continue his work as a medical student? Must be give up medicine as a career? Should he receive the classical medical treatment for his condition, namely, confinement to bed, prolonged rest, etc., or should he be at once operated upon? Compliance with either of the last two conditions practically meant for him the giving up of medicine as a career, and his apprehension was such a striking feature of the case that I concluded finally that the mental trauma inflicted, were he entirely withdrawn from his chosen work, would be so great as perhaps to do him as much harm as a continuance of the work under modified conditions.

He was directed to give up study, to attend his lectures, clinics and recitations, to go to bed at a regular time each night, and to force his nourishment to the full. He was given large doses of bromide until sleep became excellent and apprehension as to his work and standing was quieted. Notwithstanding these restrictions, he was able to pass his examinations very satisfactorily at the end of the year and was then directed to spend the

summer entirely away from medical work. His necessary occupation during the vacation was largely a matter of physical strain only and the work was so easy nervously for him that he was advised to continue it, but to eat regularly, play baseball, and to go to entertainments as much as circumstances permitted.

He returned to school in the fall much improved, though under mental excitement, considerable degrees of tachycardia still developed. His work during the fourth year was almost entirely practical and clinical, and was much enjoyed. He was again advised to study as little as possible, but to attend his clinics and all class exercises regularly, to go to bed early, and to eat as generously as possible. He gained steadily throughout his fourth year and graduated high in his class, making easily the hospital to which he aspired. Bromides had long ago been discontinued and he gained constantly in flesh and self-assurance while in the hospital, though it was occasionally necessary for him to curb himself when he was tempted to work too hard or for too long hours.

After leaving the hospital he entered independently into general practice, switching his chief attention toward surgery. His practice developed rapidly and in the hospital to which he had attached himself he rapidly passed the periods of assistant and assistant attending surgeon and now, at the age of twenty-seven years, he is a full visiting surgeon, with his entire work given over to surgery in which he is doing quite all that he is able to do. He is robust, happy in his work and success, enjoying life immensely, and no signs of disease of the thyroid are now evident unless it be a very quick emotional response and an almost abnormally quick acquisition of knowledge and technic.

I consider this case a typical example of hyperthyroidism excited by an abnormal demand placed on the gland by the conditions of life, as a result of which pathological symptoms developed. With a cessation of the abnormal demand a diminution in secretion took place and with the resumption of a relatively normal life, at least as much as a busy practitioner can expect, a return to normal followed. I am also of the opinion that the winning personality, tremendous capacity and virility of this young man are to a considerable extent the natural results of a very quick thyroid response. Many similar, though few so

marked, examples have come under my notice as a teacher of medical students. One further example only will be cited.

At the conclusion of my lectures on the endocrine organs the last college year, a young man came to me for advice as to his own condition. His history in general was uneventful except that since early childhood he had been a confirmed and successful student. Though fond of outdoor sports and a typical boy in every respect, mischievous, alert, and attractive, he had given most of his time to study and had rapidly passed his regular college course and entered medical college, where he found his work so absorbing and interesting that he "found little time to get into trouble," as he himself expressed it.

When he came to me he was suffering very much from tachycardia, especially when under nervous stimulation; and though fully aware of his ability, he was very apprehensive when called upon to recite. He showed an asymetrical goitre, which he asserted was increasing in size. He was losing flesh rapidly, had ceased to sleep normally, had marked periods of depression and of nervous incoordination, marked dermographia, and he felt himself fast slipping into a condition which he described as "neurasthenia."

Much the same regime as in the previous case was instituted; the boy was advised to accept neither operation, x-ray exposure nor even medical treatment, except the use of bromides at night, to have as much diversion as possible, music, play, plenty of sleep, outdoor exercise, and as much neglect of his studies as was possible, while attendance at classes, recitations and especially his clinics was urged. He succeeded in passing his final third year examination satisfactorily, but was forbidden to enter a hospital, as he had expected to do that summer. He was urged instead to go to the country and work on a farm or ranch until college reopened in the fall, giving his entire time and attention to physical activities and to recreations along the same line. He had gained rapidly in weight during the last semester, the tachycardia had greatly diminished, both in severity and in frequency, he had been again able to sleep normally and was greatly improved in all respects. Meanwhile the goitre had diminished so much in size that it now entirely failed to attract attention. He returned from his vacation this fall apparently

a well-balanced, healthy young man, and will, I fully believe, be entirely able to "carry on" in the medical profession.

I have also observed frequent instances of this syndrome among young women, particularly in finishing schools of the better class and in women's colleges. In most of them, however, there appears to have been an association of sexual and emotional factors which could not be elicited with the young men. I believe the condition to be the same precisely in both, but with girls at this period the disturbances of maturation are more striking and dominant than with young men. The chief concern of the latter at this period of life is usually occupational ambition or sports, while the young woman is wittingly or unwittingly thinking of love and maternity. This I believe to be the only essential difference.

By no means all of the cases of this class which I have observed have gone on to recovery and a successful life. Many have broken nervously and become neurotics; several have developed typical and persistent Graves' disease, which has responded only to aggressive treatment. The deciding factor, so far as I can judge, is very largely the intelligence with which the case is first managed.

One of my young women, whom I had considered as a very promising case and in whom the condition had apparently developed as a direct result of great sorrow, lack of affection on the part of a remaining parent, became entirely disoriented with the sane and proper school atmosphere under which she had been placed. Gifted, as most of these people are, with very considerable artistic understanding (temperament, if you like), this young woman adopted the career of a motion picture actress in which she displayed decided ability. Later, however, she developed a condition of melancholia, interspersed with emotional and temper outbursts which ruined her life and caused her, in the early twenties, to become a disagreeable, unhappy, embittered, and useless person.

Other instances of young women who have had unfortunate love affairs or contracted unhappy marriages, or in whom elected or enforced sterility has finally caused obsessions of all sorts to develop, have become hopeless misanthropes and neurotics, anathema to their physicians. Some embittered by disappoint-

ments and grief, unhealthy and unhappy, unable to find rest and satisfaction anywhere, have become the sort of old maids described in story books.

In so far as I have observed these cases, I am convinced that in very few, if any, do Freudian impulses figure to any extent. They have been simply temperamental and unusually capable and acquisitive young persons in whom an unbalanced or improper habit of life has caused an unusual demand upon the thyroid and doubtless also on other glands as well. Once established, this increased thyroid demand becomes more or less a gland habit and persists until it becomes a pathologic condition. I believe that most such cases can be brought back to normal by proper management, which must include both social and medical, and to a certain degree mental readjustments, provided, of course, these attempts receive the cooperation of the patient and are established sufficiently early before the body habits have been fully developed and fixed.

I would separate these instances very sharply from those of neurocirculatory asthenia, with which they have doubtless been often confused. I would base the essential distinction on the fact that the subject of neurocirculatory asthenia is abnormal in many other respects and these cases are undoubtedly of familial or congenital origin. There is usually associated with them a distortion of the moral perceptions, in many instances, a timorousness almost pathological, and almost without exception, there are sexual inadequacies or perversions and disinclination toward a normal physical expression in all channels. While I am convinced that in all of these cases a hyperthyroidism exists, either as an etiological factor or a sequence, it certainly is not the sole endocrine abnormality, nor the basic one. This, on the contrary, I believe to be the essential factor in the condition of physiological hyperthyroidism which I have been attempting to describe. I have never seen typical neurocirculatory asthenia develop into Graves' disease, but this is the legitimate outcome of improperly managed cases of the condition to which I am now calling attention.

I think that I have made clear my conception of this condition: that it is brought about by an abnormally great demand on the thyroid as the result of developmental growth associated

with too much emotional output. When these factors are either diminished within normal limits or directed into other channels, automatically the over-action of the gland, together with other secondary factors that may be associated with it, drops toward the normal; but if the urge is too long continued, or if fixed habits of demand and response be established, the condition will develop either into Graves' disease or take on a neurasthenic phase likely to ruin the life of the individual. It appears, then, to be but a normal response to an exaggerated or abnormal demand, with the final establishment of a tissue habit.

My purpose in presenting this study has been to point out that these instances of thyroid activity do not call for surgical or other radical treatment. On the contrary, I believe that when these are enforced serious permanent harm is likely to result,—either a subsequent hyperthyroidism or an alteration or holding in abeyance of natural and normal tendencies which, when compared to mediocrity, in their full efflorescence lie very close to genius. A failure to comprehend and correctly manage these cases leads to Graves' disease, to neurasthenia or eventual nervous and physical inadequacy.

DEGENERATIVE CHANGES IN THE SEMINAL EPITHELIUM AND ASSOCIATED HYPERPLASIA OF THE INTERSTITIAL TISSUE IN THE MAMMALIAN TESTIS

(With 5 figures in text)

ALBERT KUNTZ

Department of Anatomy, St. Louis University School of Medicine

INTRODUCTION

Degenerative changes in the mammalian testis, due to a wide variety of causes, have been described by a number of observers. Such changes involve primarily the seminal epithelium. However, not infrequently degenerating testes also show hyperplasia of the interstitial tissue, and such hyperplasia has been interpreted as an accompaniment or a result of the degeneration of the seminal epithelium. The writer ('19) has recently described degenerative changes in the seminal epithelium and associated hyperplasia[1] of the interstitial secretory tissue in the testis of the dog, following elimination of the sympathetic nerve supply to the testes and unilateral ligation and resection of the ductus deferens.

The present paper embodies the results of further experimental studies undertaken in an effort to determine whether the degenerative changes which occur in the testes following operative procedures are the direct results of these operations, or whether, in some instances, they may be but an expression of the physiological state of the experimental animal. The results of these studies also throw some light on the problem of the compensatory hyperplasia of the interstitial secretory tissue and the relationship of the hyperplasia of this tissue to changes going on in the seminal epithelium. As recorded in the previous paper referred to above, bilateral degeneration of the testes followed both the elimination of the sympathetic nerve supply to these

[1]The word, hypertrophy, has been commonly employed to designate the increase in the interstitial tissue in the testis. It was employed in the same sense by the present writer in his earlier paper. Inasmuch as the increase in the interstitial tissue which is associated with degenerative changes in the seminal epithelium involves an actual increase in the number of cellular elements it is more correctly designated as hyperplasia. The word, hyperplasia, will be employed in this sense in the present paper.

glands and the unilateral ligation and resection of the ductus deferens. A priori, there is no ground for the assumption that degenerative changes in one testis may occur as either a direct or an indirect result of degenerative changes in the other.

The dogs used in the first series were confined in relatively close quarters during the experimental period. Their diet, though ample in caloric value, was somewhat deficient in its protein content. The influence of such environment and diet can not be disregarded. For the purposes of the present study a series of rabbits and another series of dogs were subjected to operation[2] and kept under conditions as favorable as circumstances permitted. The diet of the rabbits consisted of oats, bran and alfalfa. The diet of the majority of the dogs was similar to that of the dogs used in the previous study; that of the others consisted largely of fresh meat.

RESULTS IN RABBITS

Five rabbits were subjected to operation under ether anesthesia. One of these (No. 1) was unilaterially castrated, three (Nos. 2, 3, and 4) were subjected to ligation and resection of the right ductus deferens, and one (No. 5) was subjected to resection of the right ductus deferens without ligation. The animals were allowed to live 29 to 38 days following operation. In all cases both testes, when removed, were fixed in 10% formalin and prepared for microscopic study.

In the case of the rabbit which was unilaterally castrated, preparations both of the testis which was removed at the time of operation and of the other, which remained in situ 38 days following operation, presented similar microscopic pictures, Both glands were entirely normal in all respects. There was no evidence of any increase in the interstitial tissue in the testis left in situ after unilateral castration; consequently, compensatory hypertrophy or hyperplasia of this tissue did not take place.

In all three rabbits which were subjected to ligation and resection of the right ductus deferens, the seminal epithelium of the right testis underwent degeneration with accompanying hyperplasia of the interstitial secretory tissue, while the left testis

---

[2]The operative work involved in this study was carried out by Dr. J. E. Thomas, to whom the writer desires gratefully to acknowledge his indebtedness.

suffered no apparent change. Spermatids and spermatocytes were still present in small numbers in some of the tubules while they were absent in others. The spermatogonia were materially reduced in number in all the tubules. The nuclei of the majority of the sustentacular cells remained in situ. The interstitial secretory tissue was markedly increased and showed evidence of heightened functional activity. Some of the sections also showed evidence of a slight increase in the interstitial connective tissue.

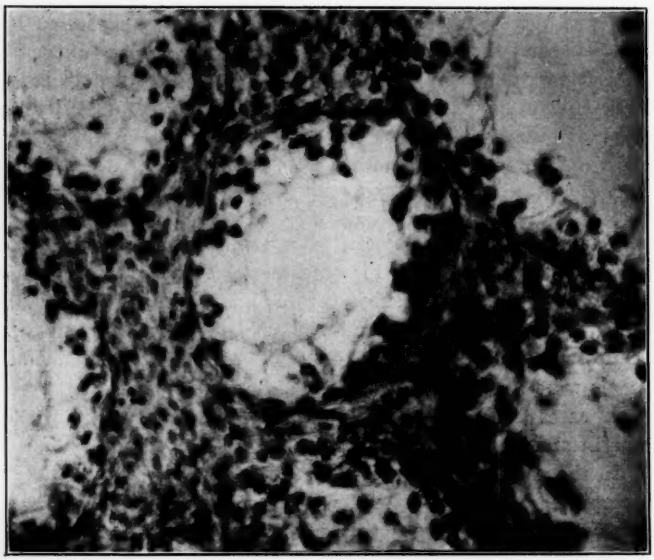


Fig. 1. Photomicrograph (x 230) of an area of a section of the right testis of rabbit No. 4 which was removed 31 days after ligation and resection of the right ductus deferens, showing degeneration of the seminal epithelium and hyperplasia of the interstitial tissue.

Limited areas of sections of the right and and left testis respectively of rabbit No. 4 are illustrated microphotographically in figures 1 and 2. This animal was allowed to live 31 days following operation until the other testis was removed. As illustrated in figure 1, the seminal epithelium of the right testis underwent advanced degeneration, accompanied by marked hyperplasia of the interstitial secretory tissue and less marked hyperplasia of the interstitial connective tissue. The relatively

small amount of interstitial tissue present in the normal testis of the rabbit is illustrated in figure 2. The testis on the unoperated side, in these rabbits, was not apparently affected by the degenerative changes going on in the testis on the operated side.

In the rabbit (No. 5) which was subjected to resection of the right ductus deferens without ligation the proximal portion of the ductus remained patent; consequently, the right testis did not undergo degenerative changes. Microscopic preparations of both testes in this case indicate that the glands were normal in all respects.

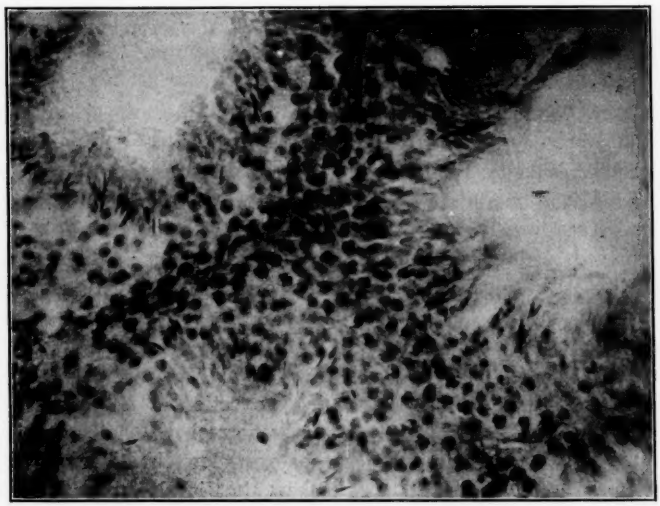


Fig. 2. Photomicrograph (x 230) of an area of a section of the left testis of rabbit No. 4 which was removed 31 days after operation on the opposite side, showing normal condition.

In this series of rabbits degenerative changes occurred only in those testes of which the outflow of the seminal secretion was prevented. The intraglandular pressure caused by the occlusion of the ductus deferens doubtless is the direct cause of degeneration in these glands. Inasmuch as none of the other testes suffered degenerative changes there is no evidence which indicates that other factors played any part in the results observed in these cases. Degeneration of the seminal epithelium is in every

instance accompanied by hyperplasia of the interstitial secretory tissue. The degree of such hyperplasia obviously is correlated with the degree of degeneration of the seminal epithelium.

RESULTS IN DOGS

The series of dogs used in this study consisted of ten animals which were subjected to operation under anesthesia and several controls. Four (Nos. 3, 7, 9, and 11) were unilaterally castrated, four (Nos. 2, 5, 10, and 12) were subjected to unilateral ligation and resection of the ductus deferens, and two (Nos. 1 and 6) to unilateral resection of the ductus deferens without ligation. These dogs were allowed to live 28 to 142 days following operation. In all cases both testes were fixed in 10% formalin and prepared for microscopic study.

In two of the dogs which were unilaterally castrated (Nos. 9 and 11) no degenerative changes took place in the testis which was left in situ following the operation. One of these dogs (No. 9) was operated under novocain anesthesia and given a diet consisting largely of fresh meat until the testis left in situ was removed 35 days later. Microscopic preparations of both testes in this case indicate that they were normal in all respects at the time of removal. The other dog (No. 11) was operated under ether anesthesia and was kept and fed with other laboratory animals for 142 days, when the right testis, which had been left in situ, was removed. Microscopic preparations of the left testis in this case show that it was entirely normal at the time of its removal, but that spermatogenesis was at low ebb. Microscopic preparations of the right testis show that it also was entirely normal at the time of its removal and that spermatogenesis was going on actively. No changes involving the seminal epithelium could be observed. Neither was the interstitial secretory tissue more abundant than in the left testis. Although this gland alone remained in situ for an interval of 142 days, no compensatory hypertrophy or hyperplasia of the interstitial secretory tissue took place.

Both the other dogs which were unilaterally castrated suffered testicular degeneration. One of these (No. 7) was killed 48 days after the right testis had been removed under ether anesthesia. Microscopic preparations of the right testis indicate

that it was normal in all respects and that spermatogenesis was going on actively. Microscopic preparations of the left testis, which was removed at autopsy, showed advanced degenerative changes in the seminal epithelium with accompanying hyperplasia of the interstitial secretory tissue. Spermatogenesis had ceased in this gland. Many of the tubules showed complete absence of spermatids and material reduction in the number of spermatocytes. Relatively few spermatids were still present in some of the tubules, but all the tubules showed unmistakable evidence of degeneration. The other dog (No. 3) was killed 36 days after the right testis had been removed under morphine and ether anesthesia. Microscopic preparations of the right testis in this case showed some evidence of degenerative changes. Apparently spermatogenesis was at very low ebb. The majority of the tubules showed very few spermatids and a material reduction in the number of spermatocytes. Sloughed epithelial cells also were present in the lumina of the seminiferous tubules and the ductus epididymis. There was no evidence of any hyperplasia of the interstitial secretory tissue. Preparations of the left testis, which was removed at autopsy, showed advanced degenerative changes in the seminal epithelium accompanied by marked hyperplasia of the interstitial secretory tissue. The evidence also indicates a slight increase in the interstitial connective tissue. Obviously, testicular degeneration was initiated in this animal before he was subjected to operation; however, the process advanced rapidly in the testis left in situ following operation. Inasmuch as the animal was apparently in good physical condition at the time of operation as well as throughout the experimental period, no cause for the early initiation of testicular degeneration can be assigned.

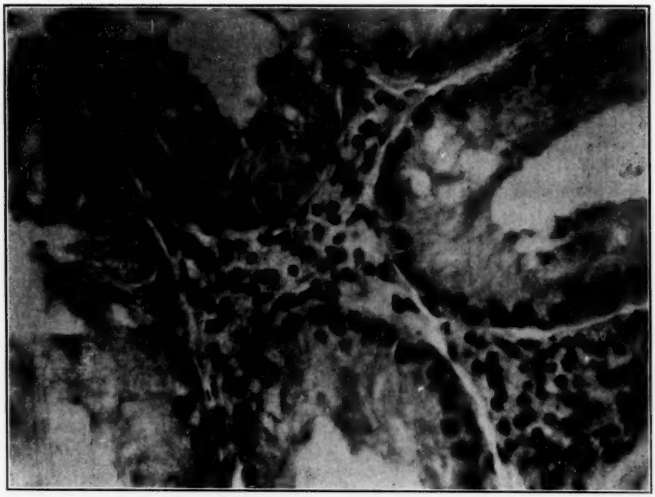
In all but one of the dogs which were subjected to unilateral ligation of the ductus deferens the testis on the corresponding side underwent degenerative changes. In the two cases in which the ductus deferens was not ligated it nevertheless became occluded. In the single case (No. 5) in which testicular degeneration did not occur following resection of the ductus deferens, although the latter was ligated, an outlet for the seminal secretion was restored. In three cases the testis on the opposite side

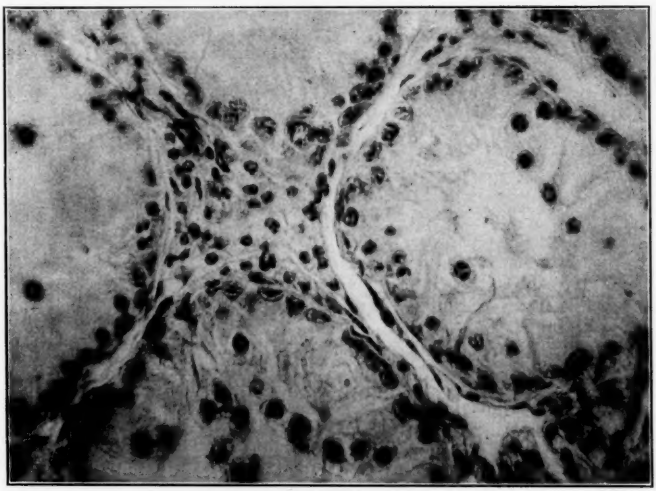
also underwent degenerative changes. In one case the evidence is not unmistakable. In the remaining two cases the testis on the opposite side suffered no degenerative changes.

In two of these animals (Nos. 1 and 6), in which both testes were removed at autopsy 28 and 42 days respectively after operation, advanced degenerative changes in the seminal epithelium with accompanying hyperplasia of the interstitial secretory tissue had taken place in both testes. Microscopic preparations showed absence of spermatids and spermatozoa in the majority of the tubules and material reduction in the number of spermatocytes in all the tubules. The degenerative changes in the seminal epithelium, as well as the hyperplasia of the interstitial secretory tissue, were not appreciably less marked in the testis on the opposite side than in the one of which the ductus deferens was occluded. The conditions observed in the right and left testis respectively of dog No. 1 are illustrated microphotographically in figures 3 and 4.

One of the dogs (No. 10) which were subjected to unilateral ligation and resection of the ductus deferens was among those whose diet following operation consisted largely of fresh meat. Active spermatozoa were expressed from the resected ductus deferens at the time of operation. Both testes were removed 35 days later. Microscopic preparations of both testes showed almost entire absence of spermatozoa and some degeneration of the seminal epithelium. The epididymis on the operated side was greatly distended. The lumen of both the right and the left ductus epididymis contained masses of sloughed cells. The degenerative changes were less advanced in the testis on the unoperated than in the one on the operated side, but hyperplasia of the interstitial secretory tissue was apparent in both.

In one case (No. 2), although the animal was allowed to live for 60 days following operation under morphine and ether anesthesia and the resected ductus deferens remained occluded, very little degeneration of the seminal epithelium and no hyperplasia of the interstitial secretory tissue occurred. However, spermatogenesis was at very low ebb. This condition probably obtained at the time of operation; consequently, the intraglandular pressure due to occlusion of the ductus deferens did not become sufficiently great to induce pressure atrophy.





Figs. 3 and 4. Photomicrographs (x 230) of areas of sections of the right and left testes respectively of dog No. 1 which were removed 28 days after resection of the left ductus deferens, showing degeneration of the seminal epithelium and hyperplasia of the interstitial tissue.

One dog (No. 12) was allowed to live 142 days following ligation and resection of the right ductus deferens under ether anesthesia. Both testes were removed at autopsy. That the outlet for the seminal secretion on the operated side had not been restored was indicated by the great distension of the ductus epididymis on that side. Nevertheless, microscopic preparations of both testes indicated active spermatogenesis and appeared entirely normal in all respects except that the interstitial secretory tissue in the testis on the operated side was markedly increased.

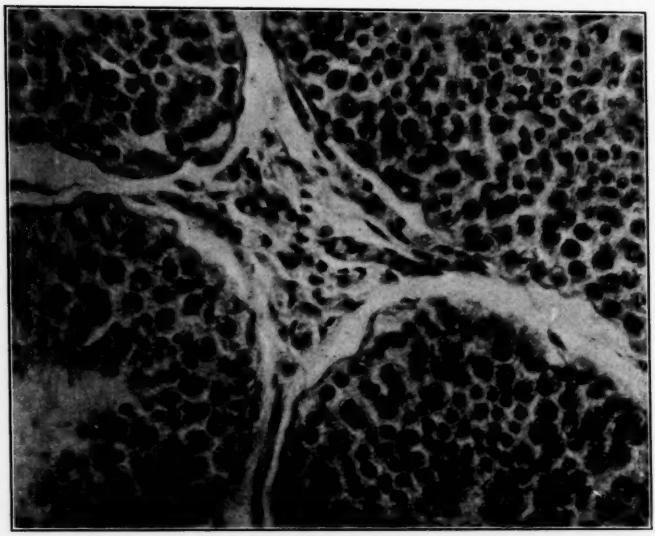


Fig. 5. Photomicrograph (x 230) of an area of a section of the right testis of dog No. 12 which was removed 142 days after ligation and resection of the right ductus deferens, showing restoration of the seminal epithelium.

Obviously, in this case regeneration of the seminal epithelium followed degenerative changes in this tissue with accompanying hyperplasia of the interstitial secretory tissue. The conditions observed in the testis on the operated side in this case are illustrated microphotographically in figure 5.

One unoperated dog, kept for one month with some of the operated dogs as a control animal, showed degenerative changes in both testes. Another dog was subjected, under ether anes-

thesia, to an operation not involving the genital organs and kept under essentially the same conditions as the other experimental animals for four months following operation, when both testes were removed and prepared for study. Preparations of both testes in this case showed advanced degenerative changes in the seminal epithelium; however, spermatogenesis was not entirely suspended. They also showed evidence of hyperplasia of the interstitial secretory tissue. None of the other control animals showed any evidence of testicular degeneration.

DISCUSSION

That the degenerative changes in the seminal epithelium following ligation or occlusion of the ductus deferens differ somewhat from the degenerative changes in this tissue due to other causes is well known. Degenerative changes due to occlusion of the ductus deferens involve first the spermatids and spermatocytes. Some of these cells become necrotic and gradually slough; others slough before they become necrotic. Degenerative changes due to other causes also involve first the spermatids and spermatocytes, but sloughing is a less important factor. The great majority of the cells become necrotic before they slough. This difference was discussed by the writer in the earlier paper referred to above and need not be considered further at this time. As degeneration of the seminal epithelium advances the spermatogonia also become involved. The distal portions of the cytoplasm of the sustentacular cells become involved relatively early, but the basal portions of these cells, including their nuclei, remain intact until relatively late. Indeed, in many of the tubules in which the seminal epithelium has suffered advanced degenerative changes, the nuclei only remain, either in their normal position or somewhat farther removed from the basement membrane.

The writer was led, in his earlier studies, to conclude that the degenerative changes observed in the testis on the opposite side, following unilateral ligation and resection of the ductus deferens, are identical with those observed in the testis of which the ductus deferens was occluded, and that degeneration in the former is "associated with and conditioned by" degeneration in the latter. The present study does not justify these conclusions.

The material upon which it is based shows clearly that when degenerative changes in both testes follow unilateral ligation and resection of the ductus deferens these changes are not identical in both glands. The same differences which are commonly recognized between the degenerative changes in the seminal epithelium due to occlusion of the ductus deferens and those due to other causes which do not involve pressure atrophy may be observed. The testis on the opposite side did not undergo degenerative changes synchronously with the one of which the ductus deferens was occluded in any of the rabbits nor in several of the dogs included in the present series of experimental animals. In those cases in which testicular degeneration occurred bilaterally, following unilateral occlusion of the ductus deferens, the changes observed in the testis on the unoperated side doubtless are an expression of the physiological state of the experimental animal.

The causal factors involved in testicular degeneration which is not the direct result of an operative procedure or traumatic injury may be exceedingly complex. Diet is an important factor. Testicular degeneration in rats, due to a diet deficient in the water-soluble vitamine, was recently described by Allen ('19). McCarrison ('19) also described testicular degeneration in fowls fed on milled and autoclaved rice. However, these fowls suffered from deficiency disease and showed degenerative changes also in other organs. Testicular degeneration under these conditions probably was a direct result of the disease, which was caused by the deficiency in the diet. The diet of the majority of the dogs included in the present series of experimental animals was somewhat deficient in its protein content. Some of these dogs suffered degenerative changes in the testis on the unoperated side; others did not. On the other hand, the diet of one of the dogs which suffered degenerative changes in both testes following unilateral ligation and resection of the ductus deferens consisted largely of fresh meat. This dog was in good physical condition at the time of operation and apparently remained so throughout the experimental period. Spermatogenesis also was going on actively at the time of operation, as indicated by the fact that viable spermatozoa were expressed from the resected ductus deferens. Indeed, testicular degeneration occurs

under such a wide range of conditions that it is quite impossible in many instances to determine a direct cause. It is not improbable that any condition which materially affects the physiological state of the animal may be a factor in testicular degeneration.

Seminal epithelium which has suffered even advanced degenerative changes may be restored and may resume its normal activity. Steinach ('20) has pointed out that in rats the seminal epithelium may be quite completely restored 6 to 8 months after ligation and resection of the ductus deferens. Regeneration of the seminal epithelium is indicated also in one of the dogs included in the present series. Both testes of this dog showed normal seminal epithelium and evidence of active spermatogenesis 142 days after unilateral ligation and resection of the ductus deferens. The great distension of the ductus epididymis on the operated side in this case indicates that the ductus deferens remained occluded. Inasmuch as in all other cases in which the ductus deferens remained occluded the seminal epithelium underwent degeneration, it is highly improbable that degeneration should not have occurred in this case. An appreciable hyperplasia of the interstitial secretory tissue also suggests that the seminal epithelium had undergone degenerative changes. Obviously this gland became adjusted to the new conditions of intraglandular pressure resulting from occlusion of the ductus deferens.

Throughout the entire series of experimental animals used in this study hyperplasia of the interstitial secretory tissue was observed as a constant accompaniment of advanced degenerative changes in the seminal epithelium. On the other hand, hyperplasia of this tissue did not occur in the testis left in situ in any of the animals which were unilaterally castrated, unless the seminal epithelium suffered degenerative changes; i. e., compensatory hyperplasia of this tissue due to the absence of the testis on the opposite side did not occur, although much more time was allowed than is required for the hyperplasia of this tissue to become well marked in glands in which the seminal epithelium undergoes degenerative changes. Hyperplasia of the interstitial secretory tissue in a cryptorchidic testis, in animals from which one normal testis has been removed, has been interpreted as a compensatory process. That cryptorchidic testes commonly show degenerative

changes in the seminal epithelium is well known. Such changes in the seminal epithelium with accompanying hyperplasia of the interstitial secretory tissue in a cryptorchidic testis doubtless have been observed frequently in animals from which a normal testis was not removed. This phenomenon was observed by the writer in both the rabbit and the dog. Biedl ('13) cites with apparent approval the work of Bouin and Ancel, in which they interpreted the enormous hyperplasia of the interstitial secretory tissue following unilateral castration and ligation of the ductus deferens on the opposite side in rabbits as a compensatory process. The present study shows clearly that hyperplasia of the interstitial secretory tissue follows ligation of the ductus deferens no less promptly in the presence than in the absence of a normal testis on the opposite side. As suggested by the writer in his earlier paper, hyperplasia of the interstitial secretory tissue in all such cases as those cited above is probably not a compensatory process, but an accompaniment of degenerative changes in the seminal epithelium. Indeed, it is quite improbable, in the light of the present study, that hypertrophy or hyperplasia of the interstitial secretory tissue in the testis ever occurs as a compensatory process. On the other hand, hyperplasia of this tissue doubtless is a constant accompaniment of advanced degenerative changes in the seminal epithelium.

Although no active hormone produced by the interstitial tissue in the testis has been isolated, the theory that this tissue produces an internal secretion which is an important factor in the development of the secondary sexual characters, and that it plays an important part in the sexual life of the individual, is quite generally accepted. The work of not a few investigators affords at least circumstantial evidence in support of this theory. Histological evidence of the secretory character of the interstitial cells (cells of Leydig) is not wanting. Whitehead's ('08) studies, which are based on preparations of the testes of mammals of several types, including man, are quite conclusive on this point. His findings are corroborated by those of not a few more recent investigators. The present study also affords histological evidence of the secretory character of these cells. The results of experimental studies as well as observations on the behavior of animals with an undescended testis, the normal

descended testis having been removed, strongly suggest that sexual excitability is conditioned by the functional state of the interstitial tissue. The recent work of Steinach ('20) indicates furthermore an important relationship between the functional condition of the interstitial tissue in the testis and the sexual behavior and potency, as well as the physical vigor, of the individual, as manifested especially by senile animals in which hyperplasia of the interstitial secretory tissue is experimentally induced. Although none of the animals included in the present series had reached the age of senility nor had manifested any lack of physical vigor, several of the dogs in which hyperplasia of the interstitial secretory tissue had taken place in one or both testes showed unmistakable evidence of heightened sexual excitability.

SUMMARY

Of five rabbits which were subjected to operation under ether anesthesia, one was unilaterally castrated, three were subjected to ligation and resection of the right ductus deferens, and one was subjected to resection of the right ductus deferens without ligation. Testicular degeneration occurred following operation only in the right testes of the three animals which were subjected to ligation and resection of the right ductus deferens. Degeneration of the seminal epithelium in these cases was accompanied by hyperplasia of the interstitial secretory tissue.

Of ten dogs which were subjected to operation under anesthesia, four were unilaterally castrated, four were subjected to unilateral ligation and resection of the ductus deferens, and two were subjected to unilateral resection of the ductus deferens without ligation. Testicular degeneration occurred following operation in two of the dogs which were unilaterally castrated, but not in the others. In the two dogs which were subjected to resection of the ductus deferens without ligation the ductus became occluded. Degenerative changes in the testis on the operated side occurred in all but one of the dogs which were subjected to unilateral ligation of the ductus deferens. In the animal in which testicular degeneration did not occur following operation, the outlet for the seminal secretion was restored. In three cases degenerative changes in the testis on the opposite side occurred synchronously with those in the testis of which the ductus deferens was occluded. In the one dog which was

allowed to live 142 days following ligation and resection of the ductus deferens the seminal epithelium was restored.

Degenerative changes which occur in the testis on the unoperated side following unilateral occlusion of the ductus deferens or unilateral castration probably are an expression of the physiological state of the experimental animal.

Hyperplasia of the interstitial secretory tissue probably is a constant accompaniment of advanced degenerative changes in the seminal epithelium. It probably does not occur in any case as a compensatory process.

Dogs in which the interstitial secretory tissue in one or both testes had undergone hyperplasia showed evidence of heightened sexual excitability.

BIBLIOGRAPHY

Allen, E.. 1919. Degeneration in the albino rat testis due to a diet deficient in the water-soluble vitamine, with a comparison of similar degeneration in rats differently treated, and a consideration of the Sertoli tissue. Anat. Record, Phila., **16**, 93-117.

Biedl, Artur: 1912. The internal secretory organs; their physiology and pathology. With a preface by Leonard Williams; transl. by Linda Forster. Lond., 1912, J. Bale Sons and Dannielsson, 594 p. 8°.

Kuntz, A.: 1919. Experimental degeneration in the testis of the dog. Anat. Record, Phila., **17**, 221-234.

McCarrison, R.: 1919. The pathogenesis of deficiency disease. Indian J. M. Research, Calcutta, **6**, 275-355.

Steinach, E.: 1920. Verjüngung durch experimentelle Neubelebung der alternden Pubertätsdrüse. Arch. f. Entw. mech. der Organismen. Liepzig, **46**, 557-618.

Whitehead, R. H.: 1908. Studies of the interstitial cells of Leydig. No. 3, Histology. Anat. Record, Phila., **1**, 213-227.

———: 1909. A peculiar case of cryptorchism, and its bearing upon the problem of the function of the interstitial cells of the testis. Ibid., **2**, 177-181.

THE SPECIAL SERVICES RENDERED TO THE HUMAN ORGANISM BY THE SYMPATHETIC AND PARASYMPATHETIC SYSTEMS

INCLUDING BOTH NERVES AND GLANDS OF INTERNAL SECRETION

F. M. POTTENGER

MONROVIA, CALIFORNIA

With the increased interest which is now being manifested in the study of endocrinology and vegetative neurology, it is well for us to consider these vegetative systems in their broadest relationships to medicine and not to narrow down to the study of any single phase of the subject, no matter how interesting such phase may be.

In the endocrine glands and vegetative nerves we have the normal control of those functions of the body which are essential to the life and growth of the individual and the perpetuation of the species. These systems are interdependent and supplementary in their action, as is evident from their evolution. If we go back in the scale of evolutionary life to the point where there was no nervous system and where all body control was carried on by chemical products, we find nothing but the simplest of organisms. But as the organism became more complicated its sustenance and preservation became a matter of greater concern and complexity. Then a nervous system was developed, and this divided into two distinct components, one the somatic or voluntary system, presiding over the animal's relationship to the outside world, and the other the splanchnic or vegetative system, presiding over his internal mechanisms. The former is more or less under the control of the will; the latter not only acts independently of the will, but is able to functionate, though imperfectly, when entirely separated from the central nervous system. With this arrangement of physiological control, the functions essential to animal life can go on undisturbed, while the voluntary system adjusts the organism to its external environment.

While the voluntary nervous system, on the one hand, and the vegetative systems (composed of the endocrine glands and vegetative nervous system) on the other, are separate and distinct in their functions, they are, nevertheless, not wholly independent; neither of them can be considered alone. Sensory impulses which reach the spinal cord and brain over the somatic nerves influence the vegetative as well as the voluntary structures and the psychical system; and impulses which arise in the vegetative structures influence the somatic structures and psychical system. Furthermore, impulses arising in the physical system influence both somatic and vegetative functions. Therefore, all nervous, endocrine, and psychical impulses are more or less interdependent and interactive.

In the study of the internal secretions considerable progress has been made in those very definite diseases which are due to frank hypofunction, or hyperfunction of the thyroid and pituitary and to deficiency in the secretion of the pancreas. A considerable literature has also grown out of study of the adrenals and gonads. There remains, however, much still to be discovered, which, when in hand, should prove to be of great aid to the clinician. So far the studies of internal secretions have been directed with greatest zeal toward the relationship of these glands to growth, development and metabolism. Some investigators have fixed their attention upon the effect of increased and decreased secretions upon the mental and psychical states of the individual. The very interesting and very important relationships which the endocrine glands bear to the vegetative nervous system, however, have not appealed to endocrinologists as strongly as they should. This relationship is basic and should be most carefully studied.

Both the vegetative nerves and the endocrine glands are vegetative systems and are closely related developmentally, as well as in the functions which they perform for the animal economy. In the skeletal structures we have flexor and extensor muscles innervated by different nerves; but the vegetative structures are provided in a different manner with action and counteraction, or action and inhibition. In some structures the same nervous system produces action and inhibition of action. In those structures which are supplied by both the sympathetic and parasympathetic

systems, one of these activates and the other inhibits action. In the glands of internal secretion, too, we have glands that work in harmony and glands that oppose. The adrenals, thyroid and pituitary act in harmony, at least in the production of certain effects, and in their effect upon sugar metabolism they are opposed by the pancreas.

There can be but two kinds of results of stimulation in the muscles and glands which make up the vegetative structures: one activation, the other inhibition. It matters not whether the action be produced by the neurons of the sympathetic and parasympathetic nervous systems or by the chemical substances produced by the glands of internal secretion; there can be no other action produced. Recognizing this fact, investigators have divided the vegetative nervous system into two distinct components, and have been able in a measure to assign to each of these the sympathetic system and the parasympathetic system the particular function which it mediates. They are also attempting to divide the endocrine glands in the same manner and have made considerable progress, although there are still many gaps to be filled. It is widely accepted that the adrenals, thyroid and pituitary are glands which act with the sympathetic system; and many observers believe that the parathyroids, pancreas, and *secretin*-producing glands of the duodenum act with the parasympathetics.

This study and classification should be furthered by any conception which will add definiteness to the action of the sympathetic and parasympathetic systems.

If we liken the body to a tube we can graphically present the distribution and function of these two divisions of the vegetative system. The outer side of this tube comprises the skin and subdermal musculature and the tissues related to it; the inner side of the tube is the gastro-intestinal canal and the structures embyologically related to it; while the middle portion consists of the tissues which form the bulk of the body through which blood vessels course.

That part of the body which is under the control of the will, the skeletal muscular tissues, has to do with providing food for the organism and protecting it from danger. These structures would be helpless, however, were it not for the vegetative struct-

ures which make the providing of food and escape from danger possible by supplying the energy necessary for the purpose.

Although it may not be at once apparent, the subdermal vegetative structures (pilomotor muscles and sweat glands) belong to the protective mechanism of the body. The pilomotor muscles in some animals, such as the porcupine, have a very important protective function, as may be readily imagined. The sweat glands act along with the vessels of the skin in aiding the mechanism of defense by allowing heat to be given off during physical effort and in the presence of infections. Were it not for their heat-regulating power the organism would often be overcome during struggle.

These subdermal structures, most of the urogenital structures (which Gaskell calls the *urogenitodermal structures,* to show their relationship to the dermal structures proper) and the blood vessels are innervated by the sympathetics alone, action and inhibition of action being produced through the same system. The sphincters of the intestinal tract and bladder and the trigone are activated by the sympathetics and provided with inhibitory fibers by the parasympathetics. The glands and musculature of the enteral system, including the gastro-intestinal canal, except the oesophagus and cardiac end of the stomach, and all structures developed from it (lungs, liver, pancreas and body of the bladder) are given inhibitory fibers from the sympathetics. The parasympathetics activate the entire enteral system, including the respiratory tract, liver, pancreas, and body of the bladder, and send inhibitory fibers to the heart and sphincters. It also sends a few to the genito-urinary system.

By grouping together the structures supplied on one hand by sympathetic nerves and the sympathicotropic glands of internal secretion, and on the other by the parasympathetic nerves and parasympathicotropic glands of internal secretion, and by analyzing the effect upon the organism of their action in these structures, one can bring some order out of what otherwise seems to be chaos.

The sympathetic and parasympathetic systems, when viewed in their broad relationships, have separate and distinct functions to perform for the organism. Cannon, Crile, Brown and others have discussed certain phases of this subject. The sympathetic nervous system, with the glands allied to it—the adre-

nals, thyroid, pituitary, and possibly also the gonads—have to do particularly with growth, metabolism, and defense. This is the protective system which reacts against such conditions as pain, shock, fear, anger, rage, injury, and infections. It protects the individual against outward enemies, prepares him for resistance or flight, and sustains him during the effort. It provides the means for defense against injury, heat and cold, and infections. It is the protective system of the body and, as such, presides over the expenditure of energy.

The parasympathetic system, on the other hand, provides sustenance for the individual. It presides over the appetite and the digestion and absorption of food. It supplies all the necessary juices for digestion—salivary, gastric, intestinal, pancreatic, and biliary—and provides the digestive tube with motor power for bringing the ingested food into intimate contact with the secretions, for propelling them onward, and, finally, for ejecting the refuse from the body. Besides this, the parasympathetics, through their action on respiration, influence the oxygen supply of the body, a fact which indicates the intimate relationship which exists between respiration and digestion. The respiratory system develops as a diverticulum from the gastrointestinal tract and, aside from the latter, is the one system of the body which is activated by the parasympathetics.

There are also certain glands of internal secretion which seem to bear a more or less intimate relationship to the parasympathetic system, among which are mentioned the parathyroids, pancreas, and the duodenal glands, which produce *secretin*.

It can thus be appreciated that the parasympathetics have the activating control of digestion and the production of energy, while the sympathetics preside over the expenditure of energy. The former are largely anabolic, the latter catabolic. The former supply a limited number of tissues while the latter are widely distributed, and through the blood vessels reach every tissue in the body.

It is impossible for us, with our present knowledge, to assert that these functions of the two systems do not dovetail into each other. In fact, we should assume that they do. Both food and oxygen must be carried to the tissues where oxidation takes place, and various waste products resulting from tissue action

must be carried to their respective points of elimination by the blood vessels which are sympathetically innervated.

It might, at first thought, seem strange that a protective mechanism such as the sympathetic system, which provides the individual with the means for escape from or combat with an enemy, resisting an infectious disease or overcoming an injury, should exercise an inhibitory action upon the gastro-intestinal functions which are necessary to provide the nourishment which is the basis of the energy used for protection. This can be understood, however, in its relation to the struggle for survival which has ever gone on in animal life. There have been times when nothing but a supreme struggle was able to save the individual. To make this supreme effort all activity, which for the time being was not essential to defense, was checked that the energy might be utilized to preserve life. While digestion is essential for the maintenance of the organism and to store up energy for future combat, yet it can be stopped during severe struggle without resulting in harm unless the struggle is too long.

In combating infection we see this same inhibitory action on the part of the sympathetics in the gastro-intestinal canal: appetite lags, digestive juices are lessened in amount, and the muscle tonus throughout the stomach and intestines is lowered, with the result that digestion is slow and stagnation of the bowel contents takes place.

Nature has even provided a way for combating this inhibitory action on digestion in some instances, as may be illustrated in pulmonary tuberculosis. This is a chronic infection which, even in the active inflammatory state, often lasts for months. If such a state were accompanied by inhibition of the gastro-intestinal action during all the time that the disease is active, it would be extremely difficult to keep the patient from dying of inanition. But the lung is also supplied by the vagus of the parasympathetic system which affords reflex stimulation to the branches of the vagus supplying the gastro-intestinal tract and the glands belonging to it, such as the liver and pancreas, with the result that the inhibition exerted upon the gastro-intestinal tract is opposed and sometimes overcome to such an extent that during the severe infection with marked toxemia digestion goes on normally or with little embarrassment.

The parasympathetic nerves have little or no power to inhibit the action of the sympathetics in their defense program, but the pancreas, which is a parasympatheticotropic gland, seems to antagonize to a certain extent the adrenals and thyroid in some of their functions. This inability of the parasympathetics to antagonize the sympathetics in the mechanism of defense is evident from the fact that the principal structures of defense are not innervated in any way by the parasympathetics. The latter have no connection with the sweat glands and cutaneous circulation, which governs to so great a degree the dissipation of heat from the body and has to do with maintaining temperature. They have no influence upon the pilomotor muscles and little on the circulatory system, except that exerted upon the heart, salivary glands, tongue and penis. Furthermore, they play no part in the activation or inhibition of the adrenals, pituitary and thyroid; and probably have no control over stored glycogen that has been forced out of the liver by the sympathetics to be utilized by the defensive mechanism in case of struggle. So we may say that, while the parasympathetics provide the organism with food and oxygen, they apparently have no veto upon its use when once converted into potential energy.

While, as previously mentioned, there is a stage in the development of animal life when the organism is provided with energy only by means of internal secretions, and another in which it is supplied by both internal secretions and nerves of simple and comparatively rudimentary action, yet, as the organism becomes more complex, a complicated central nervous system is developed which is presided over by the higher centers, whose particular function it is to correlate and integrate all body activities. When this stage is reached the vegetative control by the vegetative nervous system and endocrine glands is linked with the higher centers in such a way that, while they are able to carry on their activities when wholly separated from the central nervous system, yet as long as they are connected with it they are closely and sensitively influenced by it. They are affected by physical stimuli which are transmitted to them through the somatic sensory nerves and by ideas and emotions which arise from psychical stimulation.

It is a long way, developmentally speaking, from the movements of the amoeba, the opening and closing of the oscula of

the sponge in response to the movements of the sea water, or the response to outward stimuli of the earth worm, with its simple nervous system; to the fine adjustments of man with his highly developed and minutely adjusted central nervous system. Yet, throughout all this wide gap, the same vegetative functions have been cared for in the same general manner, at first by response to chemical products resulting from glands of internal secretion and later by these and the vegetative nerves combined.

We shall now discuss briefly some of the functions which are performed for the organism by the vegetative systems as a whole.

Defense Against an Enemy. It is now evident that stimuli which affect the human body may be either of physical or of psychical origin. In defending the body against danger from without, stimuli of both types come into play, as will be evident in analyzing the process which results when the mechanism of defense is called into action. A man sees a source of danger, he is imbued with fear and decides either to defend himself or make his escape. Whichever course he decides upon he wills to bring the necessary muscles into action. This decision would be entirely useless, however, were it not for the vegetative nerves and endocrine glands. Muscles can not perform work unless they are provided with dextrose and oxygen for its oxidation. Six or eight times as much blood must pass through the muscles when they are in action as when they are at rest, in order to supply the needed energy. A certain amount of glycogen is stored up in the tissues, particularly the muscles and the liver, ready to be used at any time. If struggle be of short duration this stored supply may be sufficient for the purpose; if not, more must be provided by the ingestion and digestion of food or by transforming the body tissues into fuel substances. All of this requires oxygen, and the tissues at a given time have only about enough oxygen for their actual needs; therefore, pulmonary ventilation increases from a normal of 5 to 8 liters per minute to 30 or 50 liters per minute, or, if the struggle be exceedingly severe, to 100 liters or more per minute. This preparation is accomplished by a combination of the spinal and vegetative systems.

It may be necessary that this defense be called into action at once. This is accomplished through the higher centers. The emotion of fear and the desire for self-preservation cause

psychical impulses to be transmitted to the proper centers in the brain and cord, and, even before the individual moves a muscle in the struggle impulses are sent by way of the sympathetic centers in the brain through his sympathetic system (nerves, adrenals and thyroid), as a result of which his heart beats rapidly, carrying more blood to the muscles and brain, the glycogen is forced from the liver so it can be delivered to the muscles, the blood pressure rises to insure a more rapidly flowing stream, the coagulation power of the blood increases, ready to check the flow of blood in case of injury, his pupils dilate, his hair stands on end, and his sweat glands become active in order to eliminate the excess of heat produced in the struggle. At the same time there is an inhibition of action in the gastro-intestinal tract so that all energy may be directed for the time being to the brain, heart and muscles, which require all possible energy for the conflict. When the struggle begins these conditions are maintained as long as is necessary, or until the mechanism of defense is exhausted and the individual is overcome. As energy is used up and acids are formed in the blood, these stimulate the respiratory center and cause pulmonary ventilation to keep pace with the demand for oxygen.

Infections. So is it in infections; the struggle for the destruction of toxins, as it affects vegetative structures, is manifested through the sympathetic system,—a dry skin, lessened elimination with increased production of heat, resulting in a rise of temperature, rapid pulse, increased thyroid and adrenal action, and an inhibitory effect on the gastro-intestinal tract, as shown in a loss of appetite and a decrease in secretory and motor power of the stomach and intestines, producing slow digestion and constipation. The combat of infections is also accompanied by psychical stimuli, but these are of little or no importance in starting action in the defensive mechanism.

It will be appreciated that there is a marked difference between the body's reaction to the severe acute infections and the more chronic and milder ones. In both of these the defense may eventually break down, but we can sometimes study it more readily in the acute cases, in which the patient goes into collapse with rapid, inefficient heart muscle, low blood pressure, sweating and falling temperature. In some severe infections recovery is followed by marked asthenia. This was seen often fol-

lowing influenza during the recent pandemic. In this, as a part of the injury done to the sympathetic system, there is probably a hypoadrenia, the glands failing to recover quickly from the injury. This same condition of exhaustion of the mechanism of defense is a part of the picture in chronic infections such as tuberculosis.

Shock. Shock is another condition in which there is marked disturbance of the sympathetics. This is favored by the fact that the individual receives an injury at a time when his defensive mechanism is already weakened by such conditions as **fatigue, excitement, exposure,** or infection. The condition of the control of the vessels in shock is such as to stimulate a sympathetic paralysis. Blood pressure falls, fluid transudes into the tissues, and the capillaries are found dilated and filled with corpuscles.

Injury and Asphyxia. In conditions of injury and asphyxia it is the sympathetic system that bears the brunt of the struggle.

High Blood Pressure. Certain high blood pressures met with, particularly in women, may be due to sympathetic stimulation, and it is quite possible that prolonged harmful stimulation of the sympathetics might result in arterial degeneration.

Anaphylaxis. Anaphylaxis affords an example of a general stimulation which predominantly affects the parasympathetics. Mild anaphylaxis shows the following symptoms: Bronchial spasm and increased bronchial secretion, nausea, vomiting, diarrhea, and itching of the skin. Severe anaphylaxis shows increased motility of the intestinal tract with relaxation of the anal sphincter resulting in involuntary discharge of feces; increased activity of the bladder musculature with relaxation of the sphincter, causing incontinence of urine; perspiration; low blood pressure; fall in temperature and collapse. From this we conclude that the symptoms of anaphylaxis, except in severe cases in which the higher centers are predominantly affected, belong to the parasympathetic syndrome.

Local Parasympathetic Syndromes. Local syndromes of parasympathetic stimulation are common: hay fever, due to hyperirritability of the fifth and seventh cranial nerves; asthma, due to hyperirritability of the pulmonary branches of the vagus; hypermotility and hyperchlorhydria which may be due to hyperirritability of the gastric vagus and increased motility and secre-

tion in the intestine; and spastic constipation, due to hyperirritability of the sacral innervation of the colon. It must also be remembered, however, that a simulated hyperchlorhydria may be due to a marked stimulation of the sympathetics controlling the pylorus, which causes a contraction of the sphincter muscles thus interfering with the emptying of the acid contents.

SUMMARY

1. Physiological action in smooth musculature and secreting glands is controlled by the vegetative nerves and the glands of internal secretion, and is influenced by stimuli either of physical or psychical origin.

2. The vegetative nerves are divided into two systems, the sympathetic and parasympathetic. The glands of internal secretion may in a measure likewise be divided into those which act with the sympathetics and those which act with the parasympathetics.

3. The sympathetic nerves and the sympatheticotropic glands of internal secretion aid in the defense of the organism against such conditions as enemies from without, infection, pain, anger, injury, heat, cold, asphyxia, and shock. The parasympathetic nerves and parasympathicotropic glands of internal secretion provide the body with an appetite and the secretions—salivary, gastric, biliary, pancreatic, and intestinal—for the digestion of food, and motor power to the gastro-intestinal tube, for mixing the food with the secretions and propelling it onward, and for expelling the refuse from the body.

BIBLIOGRAPHY

Cannon, Walter Bradford: Bodily changes in pain, hunger and fear, 1915, Appleton Company.

Crile, George W.: The origin and nature of the emotions, Phila., 1915, W. B. Sanders Co.

Crile, George W.: Man an adaptive mechanism, N. Y., 1916, MacMillan Co.

Brown, Langdon W.: The sympathetic nervous system in disease, Lond., 1920, Frowde and Hodder and Stoughton, Ltd.

CHANGES IN THE ENDOCRINE GLANDS OF A TUMOR-BEARING FEMALE ALBINO RAT

FREDERICK S. HAMMETT

From The Wistar Institute of Anatomy and Biology, Philadelphia

A female rat nearly two years old and the mother of nine litters died, apparently from the effects of a large abdominal tumor. External examination showed the growth to be about 9 cm. in diameter and to be situated in the caudal portion of the abdominal cavity. An incision through the abdominal wall pierced the capsule of the tumor from which there escaped a large amount of sanguineous fluid which failed to clot on standing. Most of this fluid was unfortunately lost so that the weight of the tissue and fluid within the capsule cannot be given. The matrix of the growth was loose and spongy and easily friable under manipulation with the forceps. The interstices of the mass were filled with the sanguineous fluid. The tumor was encapsulated by a thick fibrous covering. Portions of the matrix were embedded and sectioned by the courtesy of Doctor Damaso Rivas, who is of the opinion that the growth was a non-malignant hematoma with a rather myxo-cavernous type of hemangioma.

On removal of the tumor the abdominal contents were seen to be greatly displaced cephalad and no point of intraabdominal attachment could be found. The uterine cornua were free and their distal extremities as well as the ovaries were colored a greenish black. The intestines near the liver were stained a greenish yellow, apparently by bile, while in the liver an encysted parasite was found, the nature of which was not determined. The pancreas was not obtainable. The spleen was enormously enlarged and blackened for about one-third of the distance from its superior pole. The adrenals were enlarged, soft and discolored. The kidneys were blackened in spots and friable. The thyroid was absent, though there appeared to be present a small amount of residual edematous thyroid tissue that was too small to be weighed. The femur was much shorter and thicker than the normal. This may have been due to an adaptive change

to the increased burden or to the evident lack of parathyroid tissue. In view of the general findings for the bones, the latter alternative is preferred.

The observed weights of the organs are given in the table, and for purposes of comparison the weights normally found in female rats of the same body length. The percentage difference of the observed values from the normal figures is given.

A comparison of the observed weights of the organs of a female albino rat bearing an abdominal tumor with those obtained from standard female rats of the same body length.

It will be noted that the brain and cord are much heavier than normal. Although King has found that these tissues tend to increase in water content some hours post-mortem, the changes noted here can hardly come under this category, since the animal was dissected shortly after death and the increases are much larger than those obtained by her. The increase in the weights of the lungs and heart might at first be attributed to the toxemia induced by the growth were it not for the fact that the liver and kidneys show no such changes. There was slight evidence of pneumonia. The enormous enlargement of the spleen taken together with the quantities of hemoglobin-containing fluid in the tumor indicate an extra activity of this organ.

The hypophyseal enlargement may be interpreted in part as either due to the lack of thyroid secretion, if we accept such lack as a cause of compensatory hypophyseal hypertrophy, or it may be allied with the findings of Houssay and Sekiguchi that mammary carcinoma is frequently accompanied by disorders of the hypophysis commonly associated with hyperfunction, and with the observation of Inglis of the simultaneous occurrence of acromegaly with a mediastinal tumor. Moreover, since Robertson and Burnett have shown that tethelin, the active substance of the anterior lobe of the hypophysis, tends to accelerate the growth of carcinomata, it is not beyond the range of probability that the tumor here observed was stimulated to increased growth by the possibly increased activity of the hypophysis. The alteration in the thymus can also be correlated with the growth of the tumor through the report

TABLE

Organ	Obsvd. wts. gms.	Stand. wts. gms.	Per cent diff. %
Body L. cm.	204	.....	.....
Tail L. cm.	185	180	2.8
Body Wt.	389.8	224.5	73.6*
Brain	2.080	1.868	10.1
Cord	0.743	0.609	22.1
Kidneys	1.908	1.891	0.8
Spleen	2.044	0.596	243.0
Lungs	2.330	1.298	79.4
Heart	1.508	0.876	72.1
Thymus	0.0887	.....	.....†
Adrenals	0.0718	0.0588	82.1
Pancreas	.....	.....	.....
Thyroid	0.0000	0.0352	100.0
Liver	9.66	10.94	11.7
Submax	0.433	0.424	2.1
Hypophy.	0.0175	0.0155	12.9
Ovaries	0.0248	0.0497	49.2
Humerus	0.2202	0.2645	16.7‡
Femur	0.4927	0.5740	14.2‡
Length—			
Humerus	21.7	26.9	19.3
Femur	24.4	34.6	29.3
Water Content—			
Humerus	35.6%	34.7%	0.9%‡
Femur	45.1%	37.4%	7.7%‡
Water Content—			
Brain	78.51%	78.02%	0.49%§
Cord	72.64%	69.94%	2.68%§

*Tumor included.

†No weight given in standard tables for this body length.

‡All values calculated on standard body weight.

§Corrected.

of Kaminer and Morgenstein, who claim that there is a relation between the condition of the thymus and the destruction of cancer cells by serum.

The peculiar fact that neither thyroid nor parathyroid tissue residues could be found supports the opinion that the former is one of the contributing causes to the marked increase of the epidermal fibrous tissue simulating myxedema in certain of its aspects, and that the latter had something to do with the considerable lack of development of the calcareous portion of the bones as shown by their lesser weight and length and greater water content. The lower weight of the ovaries may possibly be correlated with the hypophyseal changes (See Arai, 1920).

In cases such as this it is difficult to distinguish between cause and effect. Nevertheless the most logical assumption to be made with the data at hand is that the alterations observed are due in major part to the systemic toxemia resulting from the pathological growth; particularly since Farrant has shown that certain symptoms of endocrine disturbance in the insane can be traced to toxemias of one sort or another, and from the clinical observations of Hofbauer and Smith that both pregnancy and the toxemias of pregnancy produce hyperplasia of the thyroid, adrenals and hypophysis. Although neither kidneys nor liver gave by hypertrophy evidence of the existence of such a condition, nevertheless, we cannot deny that a toxemia was present as a product of the tumor and that it had caused the marked alterations in the endocrine glands found at autopsy.

SUMMARY

A case is described of a tumor-bearing albino rat in which marked alterations in weights of all of the endocrine glands were observed at dissection. The hypo—or hyper—function of these several tissues serves to explain some of the abnormalities observed in the other tissues, and can be correlated in part with certain clinical observations reported on man.

BIBLIOGRAPHY

Arai, H.: On the post-natal development of the ovary (Albino rat) with especial reference to the number of ova. Am. J. Anat. (Phila.), 1920, **27**, 405-462.

Farrant, R.: The causation and cure of certain forms of insanity. Brit. M. J. (Lond.), 1916, **1**, 882-883.

Hofbauer, J.: Die Bedeutung der Innersekretorischen Drüsen für die Klinik der Gravidätstoxikosen. Deutsche med. Wochnschr. (Berlin), 1920, **46**, 589.

Houssay, B. A.: Poliuria no hipofisaria en un cancer de la mama con metastasis. Reunion de Medicos del Hosp. Alvear, 1917, June 29.

Inglis, J.: Case of acromegaly with mediastinal tumor. Colorado med. (Denver), 1916, **13**, 92.

Kaminer, G. & Morgenstein, O.: Ueber Beziehung zwischen Thymus und Carcinom. Biochem. Ztschr. (Berlin), 1917, **84**, 281-331.

King, Helen D.: The Effects of Pneumonia and of Post-mortem Changes on the Percentage of Water in the Brain of the Albino Rat. J. comp. neurol. (Phila.), 1911, **21**, 147-154.

Robertson, T. B. and Burnett, T. C.: Hydroxylbenzene radical in the acceleration of growth of carcinomata by cholesterol and by tethelin. J. Canc. Research, (Balt.), 1918, **3**, 75-91.

Sekiguchi, S.: Hypophyseal disorder in mammary cancer and its relation to diabetes insipidus. Ann. Surg. (Phila.), 1916, **63**, 297.

Smith, G. E.: Fetal and Maternal Athyrosis. II. Endocrinol. (Los Angeles), 1919, **3**, 262-272.

FURTHER OBSERVATIONS ON THE PIGMENT CHANGES FOLLOWING REMOVAL OF THE EPITHELIAL HYPOPHYSIS AND THE PINEAL GLAND IN THE FROG TADPOLE

(With 4 figures in text)

WAYNE J. ATWELL

From the Laboratories of Anatomy, Medical Department of the University of Buffalo

That the early removal of the epithelial hypophysis in the frog tadpole results in the production of an individual with a greatly disturbed pigmentary system has been shown by P. E. Smith, B. M. Allen and the writer. The operated animal exhibits a much lighter color than its normal mates and has been termed a "silvery" individual or an "albino." Apparently considerable difference of opinion has existed concerning the nature of this pigmentation change and the altered condition of the various types of pigment cells which may be responsible for it. Since the publication of a previous brief contribution bearing on these points additional observations have been made and the total results are now presented in a more comprehensive form, together with photomicrographs from the living animal.

HISTORICAL

Smith ('16) states that the differences in color begin to be noticeable in the operated tadpole before a length of 15 mm. has been reached. In his paper Smith holds that "these pigment differences are referable chiefly, if not solely, to the condition of the epidermis." Counts of the melanophores of corresponding areas in the 'albino' and in the controls showed that in the epidermis the number of these cells was reduced in the former. It was further observed that the melanophores of the albino specimens contain fewer pigment granules than do those of the controls, and thus have a distinctly lighter appearance. Smith states that "the melanophores are equally expanded in the two types, consequently the lighter appearance of the albinos cannot be due to the con-

tracted condition of the chromatophores." The free pigment granules which are so noticeable in the superficial layer of the epidermis in normal animals are much reduced in the operated tadpole. The deeper or subcutaneous pigment is present in as great quantity, if not greater, than in the normal animals.

Allen ('17) noted that the color change occurs when the operated tadpole is about 8 mm. in length. He also records the observation that only a few pigment cells are to be found in the epidermis of the operated animal. It is suggested that the pigment cells have migrated to deeper positions. As regards the deeper chromatophores, he states that "there is a constant difference in that they are expanded in the normal tadpoles and much contracted in the operated ones."

At this stage of an apparent controversy the writer ('19) obtained evidence, of an experimental nature, which strongly supported Allen's contention that the lighter color of the operated tadpole is due largely to an altered state of contraction of the melanophores, rather than to a reduction in the amount of pigment material present. This evidence consisted, briefly, in the ability to darken appreciably the silvery tadpole by subjecting it to extracts or emulsions of pars intermedia, coupled with the direct observation in both living and fixed material that the deeper melanophores, which in the silvery tadpole are contracted, expand under this treatment.[1]

Smith ('19) strongly controverted the statement that the silvery tadpole may be darkened by treatment with appropriate pituitary solutions, stating that "albinous larvae have never in the hands of the writer been appreciably increased in depth of pigmentation." And in regard to the view of Allen and the author that the deeper melanophores are contracted in the silvery animal he stated: "In the experience of the writer no constant deviation exists from the various stages of relaxation or expansion which may occur normally in the subepidermal or deeper melanophores as contrasted

[1]At the time of this former brief article the writer failed to recognize that any controversy existed concerning the role of the light-colored pigment cells, the xantholeucophores. By use of the low powers of the binocular microscope their changed condition in the operated tadpole as compared with the normal is readily apparent, even to the casual observer. All statements in the previous article refer only to the melanin-bearing chromatophores.

with normal larvae.'' At this time he directed attention to the role of the silvery, or light-colored pigment cells, the xantholeucophores.[2] These cells, which are contracted and inconspicuous in normal tadpoles, are widely expanded in the operated animal. They are responsible for the metallic lustre which the silvery tadpole displays. They are held to mask, to a considerable degree, the deep melanophores and thus to reduce to a minimum any color effect which might be produced by the latter.

In his recent memoir Smith ('20) has considerably modified the views expressed by him in previous writings. In fact, he is able to confirm the writer in both of the points formerly controverted by him, admitting that ''the deep melanophores exhibit a contracted condition'' at least in the young albino, and further agreeing ''as pertains to the darkening of these larvae and the expansion of the corial melanophores when placed in the pars intermedia solution.'' He states also that in the albino tadpole darkened by immersion in pars intermedia solutions the xantholeucophores suffer a great contraction.

The prolonged feeding of albinos[3] with posterior lobe substance was found by Smith to result in a considerable degree of darkening. So far as analyzed by him, this darkening is to be accredited to the restoration of melanin granules in the epidermal chromatophores and epithelial cells. The xantholeucophores were found to be refractory and were not reduced to their normal state of contraction. The condition of expansion or contraction obtaining in the deep melanophores is not recorded.

McCord and Allen ('17) found that the normal frog tadpole is made very transparent by immersion in solutions or emulsions

---

[2]The term 'xantholeucophore' as used by Gaupp ('04) has been objected to recently by Schmidt ('19-'20) who finds that the two pigments (xanthin and guanin) exist separately in two kinds of cells, xanthophores or lipophores, and guanophores or leucophores, respectively. In the present article xantholeucophore is used to designate the pigment cell, or cells, containing light-colored pigments, without attempting to analyze the varieties. The 'interference cell' of Biederman is homologous.

[3]The continued use of the term 'albino' (Smith) seems confusing and undesirable. It is probably to be considered a relic from the time when the light color of the hypophysis-free tadpole was believed to be due principally to a reduction in the amount of pigment material. Such reduction is now known to be confined to the pigment of the epidermis. Hereafter in this article the term 'silvery' will be employed as being more accurately descriptive.

of beef pineal substance in water. A study of the pigment cells showed that the epidermal chromatophores are not perceptibly modified, but the deep melanophores undergo a very striking contraction. The effect is transitory, passing off in a few hours unless pineal material is repeatedly added. Smith ('20) confirms most of the results obtained by these observers. He notes further that the xantholeucophores are not changed from their usual state of strong contraction.

OBSERVATIONS

Pineal Solutions. Treatment of normal frog tadpoles with pineal solutions or emulsions, first done by the author in the spring of 1918, following McCord and Allen, gave results which confirmed those writers. The change by which the normal dark tadpole becomes transparent is accomplished in a short time, usually 15 minutes to one hour. The condition is transitory and disappears within two to four hours, or sooner if the tadpole is removed to fresh water. While the animal is in the transparent state the eyes, which apparently do not suffer reduction in pigmentation, are very distinct. as are also the liver and other large viscera. The animal does not display the silvery metallic lustre so characteristic of the hypophysectomized tadpole. The appearance of the animal is dull and drab and the term *ashen* has been chosen to designate it.

A critical examination of the pigment cells in the ashen tadpole discloses the following points which may be briefly summarized:

(1) The free epidermal melanin is not changed.

(2) The epidermal melanophores apparently are not changed from their normal, expanded, dark condition.

(3) The deep melanophores are reversed from their normal expanded condition to one of very strong contraction.

(4) The xantholeucophores are not modified from their normal state of marked, pin-point contraction.

Pineal Gland and Hypophysis Removal. Removal of the pineal gland alone in the frog tadpole was found to produce no change in the depth of pigmentation. Epiphysectomy under chloretone anesthesia was performed when the larvae were about 8 mm. in length. It was found that previous to this stage the cavity of the pineal is in open communication with

the third ventricle. Consequently earlier removal of the gland results in a temporary cerebral fistula. Shortly before a length of 8 mm. is attained the gland closes off from the brain and, if care is exercised, it may be removed without perforating the brain wall. Such an accident rarely proved fatal, however. Epiphysectomized tadpoles responded to treatment with beef pineal quite as readily as the unoperated.

Having in mind the effect of pineal solutions on the pigmentation of normal larvae, it was assumed, subject to experimental determination, that perhaps the main factor in the production of the silvery tadpole following hypophysectomy was an unrestrained activity of the pineal. It was held that if this be true removal of the pineal, as well as the hypophysis, would prevent the characteristic silvery condition of the hypophysis-free animal. Accordingly the double operation was performed: first the removal of the hypophysis at the stage of 3.5 to 4 mm. and six or seven days later, when the animal was approximately 8 mm. in length, the removal of the pineal. The hypothesis on which the double operation was undertaken was entirely disproved, since these tadpoles turned silvery, as well as those which had undergone hypophysectomy alone.

Condition of the Chromatophores in the Silvery Tadpole. Repeated observations made on both living and fixed material confirm the previous observations of the writer as regards the condition of the melanophores in the silvery or hypophysectomized tadpole. The amount of pigment in the epidermal melanophores is reduced as is apparently also their actual number. Some of them are contracted, or at least the pigment material is concentrated in them. The pigment granules of the epithelial cells are reduced in number, as stated by Smith. The deep melanophores exhibit various stages of contraction. They are not so uniformly or so strongly contracted as in the case of the temporary transparency of the ashen larva (normal tadpole under influence of beef pineal).

In the silvery tadpole the xantholeucophores are readily seen to be so widely expanded that the neighboring cells are almost contiguous; in the normal they are contracted to minute points. That they do not mask entirely the deeper melanophores may be seen by reference to fig. 1, which was photo-

graphed from a living tadpole 15 mm. in length. Many of the melanophores may be seen as rounded black spots. These are particularly noticeable in the vicinity of the eye and at the root of the tail. The xantholeucophores appear in this figure as relatively large irregular white spots. Their arrangement in two layers becomes more distinct when the tadpole has at-

Fig. 1. Living, unanesthetized, silvery tadpole, 15 mm. in length, photographed through one tube of the binocular microscope. The deep melanophores, strongly contracted, may be seen as rounded black spots in the vicinity of the eye and at the root of the tail. The expanded xantholeucophores show as larger, irregular white spots.

tained a length of 25 to 30 mm. It is not so apparent in the younger stages.

Objection has been made to the tail as a site for study of pigment cells, on the ground that this region is atypical. It has been our observation that the midrib (not the fin) of the tail contains the different varieties of chromatophores found in the skin of other regions of the body, that they exist in the

same relative states of contraction or expansion, and respond, to certain stimuli at least, in the same manner as those of other parts of the body. True, they are not nearly so numerous nor so richly branched as on the dorsum of the body, but this is an advantage rather than otherwise, especially in observations with high power objectives. Figure 2 represents a photomicrograph, taken by reflected light, from the midrib of the tail of a living silvery tadpole while held in a Clark chamber and immobilized by a 1:5000 solution of chloretone. Previous observations had shown that chloretone of itself does

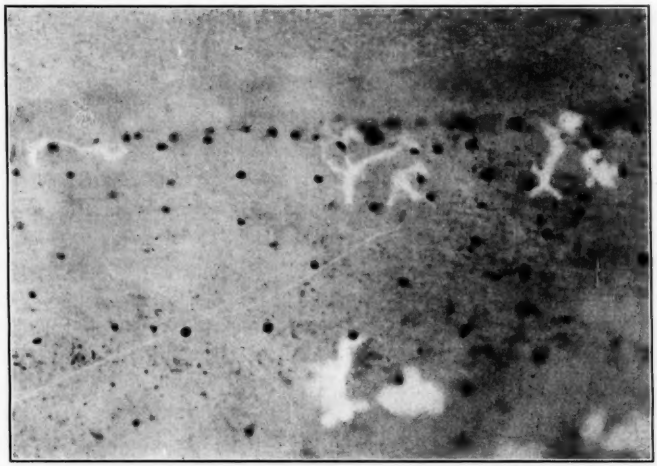


Fig. 2. An area from the mid-rib of the tail of a 16 mm. silvery tadpole, held in the Clark chamber under chloretone anesthesia; photographed with 16 mm. objective and reflected light. Deep melanophores, contracted; xantholeucophores, expanded.

not bring about the contraction or the expansion of the chromatophores, nor prevent the reactions ordinarily obtained by the use of other agents. Figure 2 shows the deep melanophores and the xantholeucophores. The former are the more numerous and exist as dense rounded spots, showing marked contraction. The latter are relatively scanty and exhibit great expansion. Their processes are often more delicate than those found in the coresponding cells of the dorsal body region. From these observations, combined with the study of *toto* skin

mounts prepared after careful fixation, the condition of the various types of pigment cells in the silvery tadpole may be summarized as follows:

(1) The free epidermal pigment is reduced in amount.

(2) The epidermal melanophores are reduced in number and apparently in pigment content. Contraction of the cells, or concentration of pigment in them, is often apparent.

(3) The deep melanophores are in various stages of contraction. They are not all in such complete contraction as may be induced by such agents as pineal gland solutions, for example, but they are definitely contracted when compared with the same cells in the normal dark tadpole.

(4) The xantholeucophores are widely expanded.

The Darkening of the Silvery Tadpole by Action of Pituitary Extracts. That the silvery tadpole may be made considerably darker for a short time by treatment with certain pituitary solutions was reported previously by the writer. Although denied by Smith at that time ('19) confirmation has recently been given by that author ('20). Further observations have verified our earlier results. It has been possible to obtain a darkening with pars intermedia substance of the beef hypophysis, with aqueous extracts of the posterior lobe prepared according to a method described elsewhere (Atwell and Marinus), and with 'oral' pituitrin (Parke, Davis and Co., serial number 2413685). Darkening did not result from dilute extracts of the anterior lobe of the beef hypophysis. It was sometimes obtained by the use of very strong anterior lobe extracts, but these proved rapidly fatal. It is possible that when the stronger extract was employed there was sufficient contamination from the posterior lobe to cause the effects seen. It was ascertained that when an appropriate strength of anterior lobe extract failed to produce darkening, the effect could always be produced by use of posterior lobe extract of the same strength. This seems to give support to the assumption that the posterior lobe is the part responsible for color changes in the silvery tadpole.

Critical observation of the living animal, unanesthetized, under the binocular miscroscope, shows that in the darkened tad-

pole the deeper melanophores are expanded. A limited, partial contraction of the widely expanded xantholeucophores has been observed in some cases. This has not in any case been great enough to be considered reciprocal to the expansion of the deep melanophores. In these temporary periods of darkening the epidermal pigment, both that found free in the epithelial cells and that contained in the epidermal melanophores, is not restored. Confirmatory results were obtained by examination of the living tadpole in the Clark chamber. It was possible to select a certain field and to study it while the animal was in the

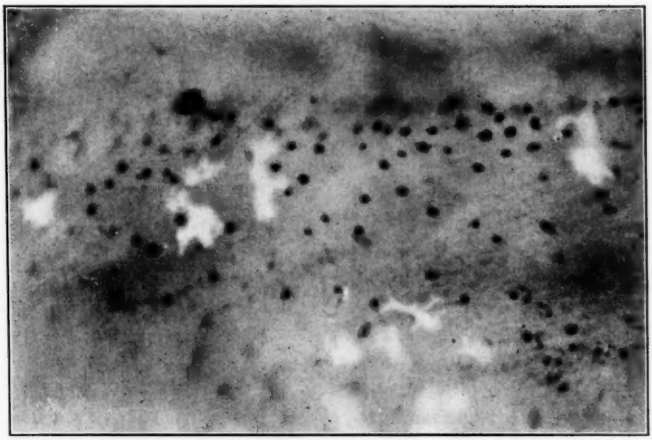


Fig. 3. From the mid-rib of tail of a silvery tadpole; same as figure 2.

silvery state and later when darkened by a 1:100 solution of 'oral' pituitrin. Photographs by both transmitted and reflected light were obtained. Transmitted light does not differentiate well the xantholeucophores from the melanophores, but reflected light brings out the two types of chromatophores in a beautiful manner. Photographs obtained with a 16 mm. objective, showing the same field before and after darkening, are presented in figures 3 and 4. The field chosen was from the midrib of the tail. Epidermal melanophores are not shown, being for the most part out of focus. In figure 3 the deep melano-

phores may be seen as numerous dense, rounded spots. The xantholeucophores are less numerous and are seen in the figure as widely expanded white cells. In figure 4, taken after the silvery tadpole had been darkened by 'oral' pituitrin, the same deep melanophores and xantholeucophores shown in figure 3 may be identified. The melanophores are seen to have expanded by sending out numerous procesess. The xantholeucophores have changed but very little, although perhaps a slight degree of contraction may be noted. This is not marked enough to be considered reciprocal to the expansion of the melanophores. The condition of the several kinds of pigment cells in the silvery

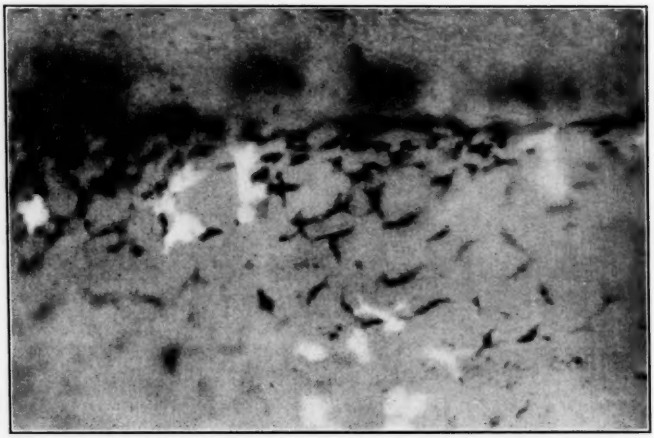


Fig. 4. Same field as in figure 3, showing change in pigment cells when animal is darkened by action of 'oral' pituitrin. Same cells shown in figure 3 may be identified. Deep melanophores are expanded; xantholeucophores not greatly changed.

larva which has been darkened by the action of pituitary extracts may be summarized briefly as follows:

(1) The free epidermal pigment is not restored.

(2) The epidermal melanophores are not restored.

(3) The deep melanophores are expanded, but ordinarily not so completely as in the normal untreated control.

(4) The xantholeucophores are perhaps somewhat contracted. This reaction is not so marked as the expansion of the melanophores.

DISCUSSION AND SUMMARY

It is evident that the appearance of a lighter color in the frog tadpole following removal of the epithelial hypophysis, is not a simple phenomenon. It is not due to the reaction of any one type of chromatophore alone. As concerns the melanin-bearing type of cell, of which there are two varieties, epidermal and deep, reduction and contraction (or concentration) occurs in the former and contraction in the latter. It is also to be noted that reduction of the amount of 'free' melanin in the epithelial cells takes place. The light-colored pigment cells or xantholeucophores become widely expanded.

In attempting to evaluate the roles of the different chromatophores in the causation of the characteristic appearance of the hypophysis-free tadpole, experimental methods have been of much value. It has been shown that when the normal dark tadpole is treated with a pineal solution the principal reaction is a contraction of the deep melanophores. The animal in this condition presents a light colored, semitransparent appearance which has been described as *ashen*. The silvery tadpole, in addition to being light colored, possesses a characteristic metallic lustre. This latter feature is due, without doubt, to the expansion of the xantholeucophores which may be observed in the silvery but not in the ashen tadpole. That the condition of the deep melanophores is of importance is amply shown by the fact that these cells are not by any means completely obscured by the expanded xantholeucophores. If the deep melanophores were not contracted the silvery tadpole would be considerably darker. In fact just such a darkening takes place when posterior pituitary extract is used. The principal reaction is found to be an expansion of the deep melanophores. The writer cannot agree with Smith that the xantholeucophores contract sufficiently to be largely responsible for the darkened appearance.

The reason why the darkened silvery tadpole is not so dark as the unoperated control is the fact that the xantholeucophores do not markedly contract, as well as the fact that the epidermal melanin is not restored in so short a time. Authors are pretty well agreed that the xantholeucophores are more refractory to the action of agents than are the melanophores. This is clearly shown by the use of pineal substance. Furthermore, the long-

continued feeding of silvery tadpoles with posterior lobe substance results in the restoration of the epidermal melanin but does not produce contraction of the xantholeucophores (Smith).

CONCLUSIONS

1. The silvery tadpole is light-colored because of the condition of its melanophores, and lustrous because of the condition of its xantholeucophores. The light color is due to the fact that the deep melanophores are contracted and the epidermal melanophores and free melanin are reduced in amount. The metallic silvery appearance is due to a wide expansion of the xantholeucophores.

2. When the silvery tadpole is temporarily darkened by the action of posterior lobe extracts the deep melanophores expand. There is in some cases a slight contraction of the xantholeucophores, but this is never complete. The epidermal melanin is not restored.

3. Removal of the pineal gland alone does not produce a pigmentary disturbance in the frog tadpole.

4. Removal of the pineal gland soon after the removal of the epithelial hypophysis in the frog tadpole does not prevent the silvery reaction characteristic for the removal of the hypophysis alone.

BIBLIOGRAPHY

Allen, B. M.: 1916. Extirpation experiments in Rana pipiens larvae, Science, Garrison, N. Y., n. s., **44,** 755-757.

———: 1917. Effects of the extirpation of the anterior lobe of the hypophysis of Rana pipiens. Biol. Bull., Woods Hole, **32,** 117-130.

Atwell, W. J.: 1919. On the nature of the pigmentation changes following hypophysectomy in the frog larva. Science, Garrison, N. Y., n. s., **49,** 48-50.

Atwell, W. J., & Marinus, C. J.: 1918. A comparison of the activity of extracts of the pars tuberalis with extracts of other regions of the ox pituitary. Am. J. Physiol., Balt., **47,** 76-91.

McCord, C. P., & Allen, F. P.: 1917. Evidences associating pineal gland function with alterations in pigmentation. J. Exper. Zoöl., Phila., **23,** 207-224.

Schmidt, W. J.: 1919-20. Ueber die sogenannten Xantholeucophoren beim Laubfrosch. Arch. f. mikr. Anat., Bonn, **93,** 93-117.

———: 1919-20. Ueber das Verhalten der verschiedenartigen Chromatophoren beim Farbenwechsel des Laubfrosches. Arch. f. mikr. Anat., Bonn, **93,** 414-455.

Smith, P. E.: 1916, a. Experimental ablation of the hypophysis in the frog embryo. Science, Garrison, N. Y., n. s., **44,** 280-282.

———: 1916, b. The effect of hypophysectomy in the early embryo upon the growth and development of the frog. Anat. Record, Phila., **11,** 57-64.

———: 1919. The pigment changes in the frog larva deprived of the epithelial hypophysis. Proc. Soc. Exper. Biol. & Med., N. Y., **16,** 74-82.

———: 1920. The pigmentary, growth and endocrine disturbances induced in the anuran tadpole by the early ablation of the pars buccalis of the hypophysis. Amer. Anat. Mem., Phila., 1920, No. 11, 1-151.

Book Reviews

INNERE SEKRETION UND DEMENTIA PRAECOX. By Oscar Lessing, Berlin, 1920. S. Karger, 63 p.

The first 35 pages of this little book are devoted to the symptomatology of dementia precox. In the last 28 pages the author tries to prove the polyglandular origin of the disease. It is a well known fact that schizophrenics may lose weight more rapidly than other patients. Even in patients who eat normally, the loss of weight may be enormous. The involuntary nervous system is often disturbed. The reaction after injection of atropin or pilocarpin is not the same as in normal subjects. The pupils are often larger than normal. Many of these patients acquire tuberculosis; this disposition is, according to Lessing, also due to endocrine disturbances. The injection of adrenalin does not cause an increased blood pressure; in 50 per cent of the cases no effect is seen when 1 cm. of a solution of 1:1000 is injected; in the other 50 per cent the blood pressure is lowered. When the serum is subjected to Abderhalden's test the reaction is positive with brain, with **testicle** in men, and with **ovary** in women. The test is often positive with **thyroid.** The coagulation of the blood is retarded; this is a symptom of hypothyroidism. Many authors state that thyroid treatment gives good results in this disease. The book is very readable but the author postulates as absolute facts various statements that have been denied by other investigators. For example, most medical men have never seen any significant effect from organotherapy in dementia precox.—J. K.

DIE MEHLFRÜCHTEKUR BEI DIABETES MELLITUS. By Prof. Dr. W. Falta, 1920, Berlin and Vienna. Urban & Schwarzenberg, 388 p.

The title of the book is not very well chosen, since many other subjects besides that indicated in the caption are treated. The term "Mehlfrüchte" is given by the author to the treatmen of diabetes by a diet rich in farinaceous elements but poor in protein. It is not essential what kind of flour is given —in fact, many different kinds can be given together. In this respect the treatment differs from the oats diet and the

diet of rice, potatoes, etc., in which only one kind of carbohydrate is given. It also differs in the fact that Falta gives his carbohydrate treatment for a long time, with an occasional fasting day or vegetable day. This treatment has been found to be suitable, not only for serious, but also for light cases. In the latter, however, more proteins may be given. The results of the treatment appear to have been very good. One case in particular is worthy of mention. A woman was brought to the hospital in coma. She rallied from this and was given Falta's treatment. Some time later she became pregnant and during pregnancy fell into coma and again recovered under the same treatment. At term she was delivered of a normal child.

The book is well written and readable, and will be found of interest to any one devoting himself to the treatment of diabetes.—J. K.

THE PIGMENTARY, GROWTH AND ENDOCRINE DISTURBANCES INDUCED IN THE ANURAN TADPOLE BY THE EARLY ABLATION OF THE PARS BUCCALIS OF THE HYPOPHYSIS. By P. E. Smith, University of California. American Anatomical Memoirs, No. 11, 1920, 112 p. and 19 plates, one in color.

The operation for the early and complete removal of the epithelial hypophysis from the amphibian tadpole as perfected independently by Smith and Allen in 1916 has provided an excellent material for the study of a vertebrate which presumably has never possessed a functioning pituitary gland. Evidence of an altered metabolism in the operated animal is the development of a characteristic silvery or "albinous" appearance. The present monograph has afforded the author opportunity not only for presenting the results of his own extensive studies on the altered anatomy and physiology of these pituitary-free "albinos," but also for a consideration of the related researches of Allen, E. R. and M. M. Hoskins and Atwell. Changes in the pigmentary system, growth disturbances and modifications in the size and structure of the other endocrine organs resulting from the operation receive thorough consideration in this comprehensive and well-illustrated memoir.

As now stated, Smith's views as to the altered condition of the pigment responsible for the "albinous" appearance of the operated tadpole are considerably modified from those set forth in his earlier articles. He finds that an actual reduction of pigment material in the "albino" as compared with the normal tadpole occurs only in the "free" epidermal pigment

and the epidermal melanophores. He also finds that the deep melanophores are contracted, at least in the younger animals, which he had apparently previously denied. The silvery pigment cells, or xantholeucophores, are widely expanded and are held to be largely responsible for the characteristic "albinous" condition.

Striking evidence that the color change is due to hormone action and not to nervous influences was obtained by effecting reciprocal epidermal transplants between "albinous" and normal tadpoles. The chromatophores of the skin area thus transplanted quickly assume the state of contraction or expansion characteristic of the corresponding cells of the host.

Of a variety of diets tried only one—posterior pituitary substance—accomplished a permanent darkening of the "albino." Confirming a previous observer Smith finds that a temporary darkening is obtained by immersion of the silvery tadpole in a pars intermedia solution. This proved to be the only physiological or pharmacological agent which would cause the return of the pigment cells to a condition approximating the normal. The evidence thus acquired indicates that the pigmentary disturbances are due to the absence of a functional posterior lobe (neural lobe plus pars intermedia).

The "albino," when maintained on a "standard" diet consisting of liver and boiled lettuce, exhibits a retarded growth curve when compared with his normal mate on a similar diet. A continuous diet of fresh anterior lobe of the beef pituitary was found to replace the growth-"maintaining" substance lost by buccal hypophysectomy and so to effect a nearly normal rate of growth in the "albino." As the author points out, the readiness with which the operated tadpole responds to the growth-"maintaining" substance of the anterior lobe makes it possible to test in a particularly efficacious manner any hypophyseal fraction for the presence or absence of this principle. Applying this test it was found that the growth-"maintaining" substance is absent from aqueous and alcoholic extracts of the anterior lobe and from the intra-glandular colloid, but that it is present in the residue remaining after either method of extraction.

With the absence of one member of a group of organs so closely inter-dependent as the endocrine system, it is necessary to conceive that a new relationship must arise among the remaining organs of the group if the animal is to survive for any considerable period. That such a readjusted endocrine balance exists in the typical albino is suggested by the definite modification in size and structure of the thyroid, the neural portion of the hypophysis and the interrenal and

chromaphil components of the adrenal. Changes of a lesser degree are exhibited by the epithelial bodies and the fat organ.

The thyroid is greatly reduced in bulk, due to a reduction in the size of the follicles and in their colloid content. The evidence for believing that this reduction of the thyroid is responsible for the failure of the "albino" to undergo metamorphosis is summarized.

The neural lobe of the hypophysis makes its appearance but exhibits a profound reduction in size, an atypical shape and an abnormal position in the operated tadpole. It would seem, then, that while the presence of the epithelial lobe is not necessary for the early formation of the neural portion, its absence is responsible for the failure of this lobe to attain its normal size, shape or position.

The cortical material of the adrenal gland is diminished in amount in the "albino" while the medulla appears to be increased and its individual cells enlarged. The epithelial bodies (of Maurer) seem to be diminished in size, while the fat organ, a structure which normally is largely exhausted at metamorphosis, persists in the "albino" even in conditions of extreme inanition. This latter is suggestive of the adiposity which follows hypophyseal insufficiency in mammals.—W. J. A.

BEZIEHUNGEN ZWISCHEN NEBENNIEREN UND MÄNNLICHEN KEIMDRÜSEN. By E. Leupold, Jena, 1920. Gustav Fischer, 62 p.

In this instructive little book the author discusses the relations between the adrenals and the testicles. First he weighed the adrenals and the testicles obtained at autopsies and found a constant relation between the two values. When the weights did not correspond there probably was atrophy of the testicle or hyperplasia of this organ. This hyperplasia combined with hypoplasia of the adrenals is observed when a persistent thymus is present. When the adrenals contain much fat the quantity of fat in the testicles also is generally high. All causes giving rise to a decrease of fat in the adrenals tend to diminish also the quantity of fat in the testicles. The testicle, however, generally contains less cholesterol than do the adrenals, and when cholesterol diminishes in the testicle and in the adrenals it generally is first decreased in the testicle; this proves that the adrenals have a higher function than the testicle. When saponine is injected subcutaneously into cats the cholesterin is partly removed from the cortex of the adrenals and from the interstitial cells of the testicles. In animals, extirpation of both adrenals produces, if the animal survives for some days, degeneration of

the secretory cells of the testicle. All the above mentioned facts are found in adults. In young children the relation between the gonads and the adrenals seems to be less intimate.

—J. K.

LAS GLANDULAS DE SECRETIÓN INTERNA Y LAS ENFERMEDADES DE LA NUTRICIÓN. Teoria y Practisca del Tratamiento Oporterapico de las Enfermedades del Metabolismo. By. G. Marañón, Madrid, 1920. Librería Gutenberg de José Ruiz. 3 ed., 437 p. 8°.

To those who are able to read the Spanish literature, this book of Marañón's is well known and hence calls for no extended review. The fact that it has reached a third edition in six years speaks for itself. Its contents are accurately indicated by the title. It contains a great mass of data presented in an entertaining and readable fashion. The monograph is written from a physiological point of view and is to be accordingly commended.

The question may be raised, however, whether the author is not over hospitable toward the claims of various investigators whose work has been quoted, and accordingly over optimistic as regards present-day endocrine therapy. The ultimate standing of hormone therapeusis will undoubtedly be enhanced by a rigidly critical attitude upon the part of writers in this field. That brilliant successes are often achieved cannot be doubted, but the fact should be equally emphasized that flat failures are also unfortunately common. The outstanding need in the field of clinical endocrinology is the development of clean-cut diagnostic criteria and much greater precision in therapeusis. Until these are achieved many conservative clinicians—men who are temperamentally averse to skating on thin ice—are likely to hold the entire field as unworthy of their much needed attention.

But in stressing the deficiencies of endocrinology as a branch of scientific medicine one must recognize that there is no lack of sheer ignorance of the solid data already accumulated. Illuminating is a recent article by Anders* in which the fact is pointed out that even so well marked an endocrinopathy as that of myxedema had passed unrecognized by one or more clinicians in 74 per cent of 55 cases studied.

R. G. H.

---

*Diagnosis of myxedema. Anders (J. M.), Am. J. M. Sc. (Phila), 1920, **160**, 801-808.

VERJÜNGUNG DURCH EXPERIMENTELLE NEUBELEBUNG DER ALTERNDEN PUBERTÄTSDRÜSE. By E. Steinach. Berlin, 1920. J. Springer, 68 p.

Rarely has a book on a scientific subject become as popular as this. Steinach's theory is that the sex gland increases in activity when the vas deferens is ligated. As an individual advances in age the sex gland gradually loses its internal secretion, and in order to increase the diminished function ligation of the vas deferens is necessary. There are other possible methods of stimulating function in the senile sex gland (chemical stimulation or x-ray treatment), but the surgical method is considered the easiest and most reliable. The author experimented upon rats. In ligating the vas deferens it is of great importance not to include the blood vessels of the testicle. It is therefore better (in rats) to ligate between the testicle and the epididymis. When the operation is performed in this way the effect can be observed more quickly than when the vas deferens is ligated. It may be recommended that the operation be performed by laparotomy, since only in this way can the vesiculae seminalis and the prostate before and after operation be compared. After the operation the cellulae seminalis atrophy and the organ shows the same histologic picture as a transplanted testicle. The effect of the operation is that the symptoms of senility disappear, the penis, vesiculae seminalis, and the prostate increase in size, the metabolism becomes more intense, the animals eat more, their sexual desires reappear, the potentia coeundi and generandi (sic!) is as in young animals. The thyroid and the hypophysis show a picture as seen in young animals. Unilateral ligation is sufficient to produce this effect. The same technic was employed in three old human patients who did not know the purpose of the procedure, which was performed in combination with another operation. In all three cases the effect was very good. Whether it is possible to obtain the same results in women is not yet known. Perhaps x-ray treatment in case of the latter may be useful.—J. K.

Abstract Department

Hereditary endogenous ADIPOSITY (Hereditäre endogene Fettsucht). Arnoldi (W.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1154.

Published elsewhere and abstracted Endocrinol. **5**, 132.—J. K.

ADRENAL tumor (Tumor der Nebenniere). Ambrozic (M.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1324.

Demonstration of the left adrenal of a girl of 3, with a tumor consisting of epithelium. The child had shown all the symptoms of macrogenitosomia praecox.—J. K.

Case of phäochromocytoma of the ADRENAL gland with hypertrophy of the left myocardium (Ein Fall von Phäochromocytoma Glandulae suprarenalis mit Hypertrophie des Myocards des linken Herzens). Bergstrand (Hilding), Hygiea (Stockholm), 1920, **82**, 321-335.

The tumor was an accidental finding at autopsy of a fifty-year-old woman who had died of influenza; it was two hundred grams in weight and lay in the upper part of the right adrenal. It was encapsulated by tissue enclosing the rest of the adrenal cortex. The tumor cells were, in spite of their variability, all of the same fundamental type, like epithelia (polygonal). They contained chromaphil and colloid-like globules. It is of especial interest that the heart showed a highly significant myocardial hypertrophy of the left side which weighed five hundred grams. All other organic alterations which such an enlargement of the heart might account for were lacking, from which it is conceivable that this condition was caused by a chronic hyperadreninemia as a consequence of the secretion from the tumor.

—J. A. H.

Treatment of spasms by removal of the ADRENALS (Die Extirpation der Nebenniere zur Behandlung von Krämpfen). Bruning (A.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1314-1317.

Fischer has discovered that when both adrenals are removed from an animal no spasms occur when the animal is poisoned with amyl-nitrite. There is a close relation between the adrenal system and muscle tonus. He, therefore, advises the removal of one of the adrenals in spasms. Bruning has tried this treatment, removing the left adrenal from nine patients. He preferred the left since in operating on the right side one may meet with adhesions of the gall-bladder.

He noted a marked improvement in all cases, but no cures. The time between operation and publication is not yet three months. It is doubtful whether in this short time it is possible to speak of a result. It would not be the first disillusionment in the treatment of epilepsy.—J. K.

Hydrocephalus and atrophy of the ADRENALS (Hydrocéphalie et atrophy des glandes surrénales). Cosmettatos (G. F.), Grèce méd. (Athens), 1920, **22**, 17-19.

According to Cosmettatos, who records a case of hydrocephalus and atrophy of the adrenals in a child who died twenty-four hours after birth, cases of co-existence of malformation of the brain and suprarenals may be divided into two groups, namely, those in which the congenital anomalies occur at the commencement of development of the nervous system and congenital anomalies which occur later, that is, after the appearance of the sympathetic ganglia and the chromaphile substance. In the first group the arrest of development of the nervous system entails an arrest of development of the sympathetic ganglia and consequently of the chromaphile substance also. In the second group, some morbid condition in the parents, such as syphilis, tuberculosis, or alcoholism, is responsible for the congenital anomalies in organs embryologically allied, namely, the brain and the suprarenal medulla.—Med. Sc. Abst. & Rev., **3**, 218.

(ADRENAL) Addison's disease following renal tuberculosis (Syndrome d'Addison fruste consécutif a une tuberculose rénale). Damade (R.), J. de méd. de Bordeaux, 1920, **91**, 303.

Damade records the case of a man, aged 58, who presented intense asthenia, low blood pressure, the phenomenon of the white line, digestive disturbances, and lumbo-abdominal pain accompanied by very slight pigmentation of the skin and mucous membrane. Treatment consisted in two subcutaneous injections of ½ mg. of adrenalin and 10 c.c. of glycerinated suprarenal juice by mouth. Immediate improvement resulted and the adrenalin was stopped in two days' time, but a relapse occurred a few days later and death took place after a comatose period of five to six hours. Although the kidneys were studded with gross tuberculous lesions, it was only by microscopical examination that slight inflammatory lesions were found in the medulla of the suprarenals.—Med. Sc. Abst. & Rev., **3**, 218.

ADRENAL infarction (Ueber Apoplexie der Nebennieren). Freudemann. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1275-1276.

Report of a soldier of 20 who had been gassed. He complained of headache and giddiness. As he did not improve much he was sent back to Germany after three weeks. Then he did light military service during seven weeks, complaining now and then of abdominal pains. He became suddenly ill with severe abdominal pain, abdominal spasms,

but no "defense musculaire." On the fourth day after this fever he developed herpes labialis, albuminuria, spasms in the region of the kidneys, rapid and feeble pulse, and constipation, but no vomiting. On the eighth day he lost consciousness and showed rigidity of the muscles of the neck. A diagnosis of meningitis was made. Death followed on the tenth day. The autopsy showed: endocarditis, embolism in the left hemisphere of the brain, embolism in the left branch of the pulmonary artery, and infarction of both adrenals with thrombosis of both adrenal veins.—J. K.

(ADRENAL) A case of cure of Addison's disease (Un cas de guérison de maladie bronzée d'Addison). Giraudeau (R.), Thèses de Paris, 1919-20, 31.

A case of recovery from Addison's disease is reported by Giraudeau. The patient, a man aged 39, the subject of chronic alcoholism, was admitted to hospital in November, 1901, with pronounced asthenia, pigmentation of the skin and buccal mucous membrane, diarrhoea, abdominal pains, and a feeble pulse. On January 4, 1902, he was given his first injection of suprarenal extracts, and the injections were continued for twelve days. Improvement took place in the general condition and there was a rapid increase in weight. The injections were resumed on January 27, when the abdominal pain and diarrhoea were very violent. On February 1, the pigmentation in the face had considerably diminished, and in the next two months it had disappeared from the rest of the face and from the buccal mucous membrane. In the summer of 1902 the general condition had so much improved that the patient was discharged. Apart from an attack of alcoholism, for which he was interned in an asylum in June, 1904, he was lost sight of until February, 1913, when he was admitted to the asylum again with another attack. Death took place on March 13, 1913. Apart from carcinoma of the pylorus with metastases in the liver, the only lesion found at autopsy was some scar tissue in the right adrenal, indicating the occurrence many years previously of some inflammatory condition the nature of which could not be determined. There were no signs of tuberculosis or syphilis. The case thus illustrates how a small suprarenal lesion is sufficient to give rise to the melanodermic syndrome. Giraudeau concludes that in cases in which transient suprarenal incompetence is the result of a localized inflammatory lesion, treatment may be effective, whereas it is of no avail in ceaseous tuberculosis of the suprarenals.—Med. Sc. Abst. & Rev., 3, 217.

(ADRENALS) Bilateral paralysis of the plexus femoralis with changes of the skin, as in Addison's disease, caused by an abdominal tumor (Dubbelzijdige verlamming van den plexus femoralis met huidveranderingen als bij zeikte van Addison ten gevolge van eengezwel in de buikholte). Klessens (J. J. H. M.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, 64 (II), 787-796.

A woman of 50 years complained of fatigue and pain in the right leg. Some months later all the symptoms of a thrombosis of the vessels developed; the leg became paralyzed. At the same time the other leg became affected in like manner. The whole body showed brown pigmentation, and in a few months the patient's hair had turned absolutely white. There were no symptoms of Addison's disease. There was a large tumor in the abdomen, perhaps a hypernephroma. Opportunity to determine this at autopsy was not obtained.—J. K.

The interrenal and ADRENAL system as one organ. The adrenal as a homogeneously functioning organ (Die Vereinigung von Interrenal und Adrenalsystem zur Gesamtnebenniere. Die Nebenniere als einheitlich funktionerendes Organ). Löwenthal (K.), Berl. klin. Wchnschr., 1920, **57**, 807-811.

It has been the custom of many authors to consider the medulla of the adrenal as the only part of physiological importance and to neglect the cortex. Embryology makes it highly probable that cortex and medulla belong together. In general infectious and other diseases medulla and cortex are generally affected together (the lipoids in the cortex decrease, the medulla fails to give the characteristic color reaction). After stimulating the splanchnics by "piqure" of the fourth ventricle glycosuria occurs, adrenin disappears nearly completely from the medulla and the quantity of lipoids (when examined immediately after operation) is diminished. It seems possible that a "pre-adrenin" is formed in the cortex, that it passes by the capillaries into the medulla and is transformed there into adrenin. It is said that the cortex produces the lipoid for the body, but this has not been confirmed. On the contrary, the quantity and distribution of the lipoids in the cortex depend on the quantity of lipoids in the blood. After removal of once adrenal the other shows hypertrophy, but though the blood at once contains more cholesterin after the operation, the adrenal at first contains less than before the operation, and it takes some time before the quantity of adrenin becomes normal again. The function of the cortex is to form a depot of cholesterol. Cholesterol is one of the most important substances in the defense of the body against infections. Perhaps the cortex has thus an anti-toxic function. However, this substance is not excreted. So the function of the cortex is to produce a local immunity and to protect in this way the medulla against infections. Löwenthal observed at autopsy that only in those cases in which the cortex contained lipoids did the medulla contain adrenin, though he states that not all investigators agree upon this. If, however, this is true it will be important to prescribe in serious infections cholesterol, as has formerly been done, particularly in France.—J. K.

(ADRENAL) Results of the operative treatment of hypernephromas. Michaelsson (Eric), Hygiea (Stockholm), 1920, **82**, 220-232.

The author discusses thirty cases which have been observed on the average for at least four years since operation. Seven were living from four to fifteen years after operation, four died as the result of the operation. There died from recurrences and metasteses: six within and three more than three years after the operation; ten died of other diseases, etc., five within the first year and a half. The histological picture afforded no valid indication of the biological value of the growth in question.—J. A. H.

(ADRENALS) The origin of hemangiectases. Moise (T. S.), Johns Hopkins Hosp. Bull. (Balt.), 1920, **31**, 369-373.

This paper presents the first description of diffuse hemangiectases of the liver in association with a similar process in the kidney and adrenals. The adrenals in the case reported here showed a diffuse telangiectasis. The process involved the cortex extensively and the medulla to a lesser degree. There was definite evidence of blood formation as shown by the presence of nucleated red blood cells and young cells of the myeloid series. The specimens were recovered at the autopsy of a case of general carcinomatosis from a primary tumor of Bartholin's gland.—J. F.

Histochemical researches on the ADRENAL cortex in cases of death by scalding (Ricerche istochimiche sulla corticale delle surrenali nella morte da scottatura). Righi (U.), Pathologica (Geneva), 1920, **12**, 331-332.

Death from scalding follows the loss of a certain amount of the skin—one-fourth of the surface for the rabbit, one-third for man—yet besides the lack of function and protection caused by the partial destruction of the skin, a severe strain on the organism is brought about by the absorption of the products of cellular destruction (from skin, aponeuroses, muscles and blood). Such a deep change must perforce act on the adrenal cortex, as its function is not only connected with the nutrition and development of the nervous system, but with the general metabolism. The author is not aware of any post-mortem examination of human adrenals in such caes; but some of Moschino's experimental researches have shown regressive alterations of the cortex in death after 24 hours; these are more marked in cases dying 48 hours after the burn. His technique (staining by hematoxylin-eosin) would not tend to give satisfactory results, however, with respect to the nuclei. No conclusion has been drawn by Moschino concerning the medullary substance. Righi repeated Moschino's experiments, using Nile Blue, Sudan III and other stains, and studied the results of death of rabbits 24 to 36 hours after scalding. Using control animals he came to the conclusion that scalding produces a marked swelling of the spongiocytes and increase of cholesterin and cholesterin esters. He did not study the medullary substance. The article ends by a citation from Landau's researches,

who, while agreeing with Righi as regards the final findings, states that the cortex, instead of undergoing an increase of function, is only the recipient of the increased amount of lipoids, which can no longer be normally eliminated.—G. V.

The differential white-cell count of the blood before and after surgical reduction of the ADRENALS (Ueber das Verhalten des relativen morphologischen weiszen Blutbildes vor und nach der operative Nebennierenreduktion bei Krampfkrankheiten nach H. Fischer). Schlund (F.), Deutche med. Wchnschr. (Berlin), 1920, **46**, 1273-1274.

The influence of adrenin on the blood picture has been repeatedly discussed. The contrary condition, however, the influence of subadrenalism, has not been studied. Fischer has described a new operation for the treatment of spasms. He removed one of the adrenals. Schlund examined the blood picture after this operation. He observed that the number of neutrophil leucocytes is increased and the number of lymphocytes diminished. There are fewer eosinophil cells after the operation than before. In one case the eosinophil cells disappeared temporarily.—J. K.

Hypernephroma of right ADRENAL (Hypernephrom der rechten Nebenniere). Schopper, Wien, klin. Wchnschr., 1920, **33**, 718.

A woman of 23 died suddenly without having shown any pathological symptoms. At autopsy a hypernephroma of the right adrenal was found. The tumor had grown through the vena suprarenalis into the inferior vena cava. During defecation a part of the tumor had been torn off, producing a fatal embolism of the pulmonary artery. —J. K.

Hypo- or dys-function of ADRENALS (Hypo- oder Dysfunktion der Nebennieren). Steinert, Wien. klin. Wchnschr., 1920, **33**, 765.

Demonstration of a case of retarded development in a girl of 5 years. There was hyperkeratosis of the nose with dark pigmentation. Whenever the patient was wounded the scars showed pigmentation. The skin was of a brownish color. The Pirquet reaction was negative. The mucous membranes were not pigmented. The author believes that during birth there occurred a hemorrhage into the adrenals. There are two types of cachectic children, a white and a dark type. The last-named type may be due to a hypofunction or dysfunction of the adrenals.—J. K.

Tumor of the ADRENALS in a congenital dystopic kidney (Nebennieren-tumor in einer kongenital dystopen Niere). Stephan. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1233.

Not of immediate endocrine interest.—J. K.

Some observations on ADRENIN apnoea (Algunas obervaçoes sobre a apnea adrenalinica). de Almeida (M. Osorio), Arch. de esc. sup. de agric. e med. Veter. (Nichteeroy), 1919, **3**, 65.

The intravenous injection of adrenin produces almost fatal apnoea when the dose is large. Preliminary ligation of the carotid and vertebral arteries does not prevent the appearance of apnoea.—B. A. H.

Action of iodine and ADRENIN on living surviving cells. Cervello (V.) & Levi (G.), Arch. di fisiol. (Firenze), 1917, **20**, 219-228; Arch. ital. de biol., 1919, **69**, 70-71.

Tissue cultivated in fowl plasma grows as readily in this plasma after it has been treated with iodine. In plasma treated with adrenin growth ceases sharply at the end of the second day. If the cultures are then removed to plasma containing no adrenin, activity revives in 24 hours and cell division in 48 hours.—Chem. Abst., **14**, 762.

The antagonism of ADRENIN and quinine (Adrénaline et quinine, leur antagonisme). Clerc (A.) & Pezzi (C.), Compt. rend. Soc. de biol. (Paris), 1919, **169**, 1117-1118.

From experiments on a dog the following conclusions are stated: There is complete antagonism in the cells of the bulbar vagus center between adrenin which excites and quinine which paralyzes. The drugs act in a similar way upon the heart. Upon arterial pressure adrenin is hypertensive, quinine hypotensive, but adrenin determines the hypertension by a combined cardiac and vascular action; whereas quinine causes hypotension by its cardiac depressive action which overcomes the vaso-constrictor influence characteristic of the two substances.—Chem. Abst., **14**, 3725.

(ADRENIN) A study of the cardiovascular reaction to epinephrin. Clough (Paul W.), Johns Hopkins Hosp. Bull. (Balt.), 1920, **31**, 266-273.

Clough finds that there is a marked difference in the cardiovascular reaction of different individuals to a subcutaneous injection of 1 mg. of epinephrin. The reactions observed have been classified arbitrarily, according to their intensity as, negative, moderate, marked and very marked. In a moderate reaction there was: (1) a rise of from 15 to 30 mm. in systolic blood pressure, associated usually with, (2) a fall of from 10 to 20 mm. in diastolic pressure. The striking feature of the reaction was (3) the increase in pulse pressure, which was often doubled. There was usually (4) a slight tachycardia. Other symptoms were usually mild. In marked reactions the systolic pressure rose from 30 to 100 mm. There was usually a slight rise in diastolic pressure also, and a marked rise in pulse pressure. There was sometimes glycosuria, and very often tachycardia, palpitation, pallor, mydriasis, tremor, nervousness, and anxiety. Atrophin fre-

quently exaggerated the response to a subsequent injection of epinephrin. Of 32 normal individuals, 82 per cent gave a slight or moderate response. Patients with hypertension often showed severe reactions to 1 mg. or less of epinephrin. Marked responses were obtained in 68 per cent of 22 cases, whereas they occurred in only 18 per cent of 32 normal individuals. This epinephrin sensitiveness occurred irrespective of the cause, the degree, or the duration of the hypertension. None of these patients showed evidences of significant endocrine disturbance. It seems probable that this epinephrin sensitiveness in hypertension may be only one manifestation of a general abnormal reactivity of the cardiovascular system to stimuli of all kinds, and that it need not be attributed to a hyperactivity of either the chromaphil system or of the thyroid.—J. F.

(ADRENIN) The point of attack of certain drugs acting on the periphery. II. Action on the retractor penis muscle of the dog. Edmunds (C. W.), J. Pharm. & Exper. Therap. (Balto.), 1920, **15**, 201-216.

Adrenalin caused a marked contraction, but after treatment with ergotoxin relaxation was observed.—R. G. H.

Blood changes produced by ADRENIN. Kägi (Adrienne), Folia Hematol, 1920, **25**, 107-152.

In man no constant blood changes were observed after subcutaneous injection of ½ to 1 mg. adrenalin. The most constant finding was a leucocytosis involving cells of both lymphoid and myeloid origin, but the leucocytosis was relative rather than absolute.—Chem. Abst.

(AUTONOMIC NERVOUS SYSTEM) (Zur Anatomie und Pathologie des vegetativen Nervensystems). Spiegel. Wien. klin. Wchnschr., 1920, **33**, 975.

There exists a morphological difference between the ganglia of the sympathetic system and the ganglia of the cranial autonomic system, as may be proved by the fact that the former are markedly pigmented in old age, while the latter never are. Graves' disease may be caused by a primary disease of the thyroid or by a disturbed nervous or chemical regulation. The constitution of the patient plays also an important part. In two cases of Graves' disease the author found inflammation of the cervical sympathetic.—J. K.

AUTONOMIC NERVOUS SYSTEM. The blood picture in diseases of the—and how it is influenced by drugs (Das Blutbild bei Störungen des vegetativen Nervensystems und seine pharmacologische Beeinflussung). Schenk (P.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1192-1193.

In vagotonia often a relative as well as an absolute increase of the lymphocytes may be observed. Sometimes there is a slight in-

crease of eosinophiles. In sympathicotonia there are no typical changes in the blood picture. Injection of pilocarpine is sometimes followed by a very light temporary lymphocytosis without an increased eosinophilia. Injection of adrenalin in sympathicotonia is followed by a very marked increase of the lymphocytes during the first half hour. This is followed by a neutrophil polymorphonuclear leucocytosis. The number of eosinophils does not change. The hypo- or an-eosinophilia that is observed in animals under these circumstances is never seen in man.—J. K.

(BRAIN) Experimental studies on growth. XVI. The influence of brain tissue, freed from cholesterol, upon the growth of the white mouse. Robertson (T. Brailsford) & Ray (L. A.), J. biol. chem. (Baltimore), 1920, **44**, 439-453.

There are many observations, hitherto isolated, which when taken together, point towards the nervous system as the source of very decisive stimulant of the growth of parenchymatous tissues. Two possible alternatives are offered: either the nervous system promotes the anabolism of parenchyma by the conduction of stimuli to it—the so-called "trophic influence" of nerves, or the nervous system promotes the anabolism of parenchyma by the elaboration of a catalyzer which is liberated from the nervous tissues and functions as a growth hormone.

The authors fed white mice with decholresterinized brain tissue and found that such material in doses of 36 mg. daily is without effect upon the growth of the mice. Moreover, it had been previously shown that cholesterol modifies the growth of mice by stimulating the growth of parenchyma so as to modify the time relationships and bring the growth curve for mice towards the form of the growth curve for human beings, in whom the ratio of brain weight to body weight is much higher. But the effect of cholesterol is much less even in high doses than the effect of a high ratio of brain weight to body weight. Hence if the nervous system does affect growth through the agency of a specific catalyzer or hormone, this substance must be more potent than cholesterol and must be extracted by acetone from the brain tissue together with cholesterol.—F. S. H.

CHOLIN as paristaltic hormone (Cholin als Hormon der Darmbewegung—II). le Heux (J. W.), Arch. f. d. ges. Physiol. (Bonn), 1920, **179**, 177.

With the isolated intestine atropin gives varying results. This is due to the presence or absence of cholin, "the hormone of intestinal movement." If it is present, the antagonistic action of atropin produces inhibition, but if cholin has been removed by repeated washing, atropin produces its ordinary characteristic effect, namely, stimulation.—Physiol. Abst., **5**, 236.

The lipins of human CORPUS LUTEUM. Rosenbloom (J.), Scientific Proceedings, Am. soc. biol. chem., XIV., J. Biol. Chem. (Baltimore), 1920, 41, lxxi.

Given by title only.—F. S. H.

Consideration on syphilitic DIABETES (Considérations sur le diabète syphilitic). Beguier (G.), Thèse de Paris, 1919.

Though a combination of diabetes and syphilis is frequently seen, syphilitic diabetes is exteremly rare. There are very few cases in the literature of diabetes caused by syphilitic sclerosis of the pancreas. The author first gives a review of the literature on the subject, referring frequently to the "islets of Langerhans," and reports a case himself of a diabetic woman in whom complete sclerosis of the pancreas was found at autopsy. This case does not appear very convincing. The syphilitic infection was not definitely proved; the Wassermann test in blood and cerebrospinal fluid was negative, and infection was denied. The pancreas was not examined histologically, or at least no report of a histological picture is given. Many of the neurological symptoms, such as loss of reflexes, may be observed also in non-syphilitic diabetes. Diabetic neuritis and the pseudotabes diabetica are well-known clinical pictures. On the other hand, the diabetes, as described by the author, was certainly not a classic case. Such a serious one, dying in coma but never showing any signs of acidosis, can not be identified with the ordinary diabetes ending in coma diabetica.—J. K.

The influence of work on the sugar of blood and urine in DIABETES (Ueber die Wirkung der Arbeit auf Blut und Harnzucker beim Diabetiker). Bürger, München. med. Wchnschr., 1920, 67, 1278.

In diabetes muscular activity increases the blood sugar. It depends on the amount of glycogen in the liver. Women show hyperglycemia more than men; young people sooner than adults. When 10-20 grams of sugar are injected intravenously then the increase in sugar in the plasma of the blood is higher at rest than when the injection has been preceded by muscular activity. Glycosuria does not depend upon the amount of blood sugar. The author observed six cases in which a rise of blood sugar was accompanied by a disappearance of sugar from the urine.—J. K.

Cholesterinemia in DIABETES (Cholesterinaemie bij diabetes mellitus). Boom (B. K.), Inaug. Diss. (Amsterdam), 1920.

From numerous observations the author concludes that there is no relation between acidosis and the quantity of cholesterol in the blood plasma. In patients younger than 40, the amount of cholesterol is generally much higher than in older patients. No relation was found between the tolerance for carbohydrates and the quantity of cholesterin. Diet was noted to have no influence—even after pro-

longed fasting the cholesterol content may remain high. Similarly, no relation is found between xanthosis and cholesterol; the xanthosis is due, supposedly, to the high concentration of lipochrome in the plasma. Whether a high concentration of cholesterol is of bad prognostic significance is not definitely established. The fact, however, that this concentration is high in younger subjects in which, in general, the prognosis is poor, suggests that some relationship may exist.—J. K.

(DIABETES) Critical glycemia. Charbanier (H), J. phar. chim., 1920, 21, 177-183; Presse méd., 1920, 28, 222.

Parallel determinations of the degree of glycemia and of acetonuria, both in normal and diabetic persons, put upon a non-carbohydrate diet (the coagulum of 3 l. of milk deprived of serum), show that upon decreasing glycemia a point will be reached, called critical glycemia, at which the corresponding acetonuria rises suddenly. Upon giving carbohydrates again acetonuria returns to normal values. This work supplements Ambard's hypothesis that hyperglycemia is a mechanism, which in the diabetic compensates the disturbance in carbohydrate metabolism.—Physiol. Abst, 5, 216.

Pancreatic DIABETES and disturbed pancreatic function (Pankreas Diabetes und pankreatische Resorptionsstörung). Dresel, Deutsche med. Wchnschr. (Berlin), 1920, 46, 1154.

The patient was a man of 30. From the 18th to the 24th years he had used alcohol excessively. At the age of 25 sugar was found in his urine. After four weeks' feeling ill he came to the hospital. The feces showed typical steatorrhoea, creatorrhoea and bulkiness. The Schmidt-Kashiwado test was positive. The duodenal contents did not contain trypsin. The urine showed about 5% sugar, with traces of maltose. The blood sugar was 0.362%. The curve of blood pressure after the injection of adrenalin was the same as in sympathicotonia; this may have been caused by the loss of pancreatic function. Injection of adrenalin raised the blood sugar but little.—J. K.

The decrease of sugar in blood and urine by x-ray treatment of the adrenals in DIABETES (Ueber Herabsetzung des Blut und Harnzuckers durch Röntgenbestrahlung der Nebennieren beim Diabetiker). Dresel (K.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1240-1241.

Stephan exposed the pancreas to stimulating doses of x-ray and observed in two cases of diabetes an increased tolerance for carbohydrates and a diminished quantity of excreted sugar. That it is possible to expose the adrenals to x-ray without any harm to the other organs is proved by the experiments of Zimmern and Cottenot, who treated patients with high blood pressure in this way, often with success. Dresel tried the influence of x-ray treatment of the adrenals in diabetes. He observed that the blood sugar showed a marked de-

crease; sometimes the sugar in the urine disappeared. The treatment is harmless. Its result, however, is temporary.—J. K.

(DIABETES) Xanthosis diabetica. Hannema (L. S.), Nederl. Maandschr. v. Geneesk. (Leiden), 1920, **1**, 318-325.

The author observed a case of xanthosis diabetica. The serum was dark yellow. There was no increase in the amount of bile pigment, the color being due to a very large quantity of lutein.—J. K.

(DIABETES) Our internal sugar shortage. Hutchinson (Woods), Saturday Eve. Post. (Phila.), 1920, **193**, 16.

An interesting and popular review of the subject of diabetes.
—F. S. H.

(DIABETES) Xanthelasma diabeticorum. Van Leeuwen (T. M.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, **64**, II, 2085-2086.

Report of a case.—J. K.

Severe case of DIABETES mellitus with multiple endocrine disturbances, Lindblom (Sven), Hygiea (Stockholm), 1916, **78**, 721-764

In a 16-year-old boy, besides symptoms of diabetes there were also symptoms of **thyroid** insufficiency, e. g., poor growth of hair. The growth of hair was improved by thyroid treatment. Near the end, a high-grade lipemia of 17.55 per cent fat set in. Death occurred in coma. At autopsy there was found a marked pancreatic atrophy with decided quantitative and qualitative alterations of the neck; significant thyroid and **hypophyseal** atrophy, particularly the pars infundibularis of the latter; the adrenals were of normal weight, but in their cortex changes were seen which were indicative of a hyperfunction. The author expresses the opinion that, although hormones of the pancreas and the thyroid function antagonistically, yet the organs themselves, whether by their hormones or by way of the vegetative nerves, stimulate one another. Various observations of diabetes, Basedow's disease and acromegaly permit this assumption.—J. A. H.

The modern treatment of DIABETES (Der heutige Stand der Diabetestherapie). Richter (P. F.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1197-1200.

A general review. The author points out three differences between modern and former methods of treatmnt. Over-nutrition is now avoided; proteins are restricted and carbohydrate "cures" are administered. Of these latter Falta's "Mehlfrüchtekur" is recommended.
—J. K.

DIABETES INSIPIDUS. Stenström (Thor), Allm. sven. Lakartidn. (Stockholm), 1916, **13**, 876-888; 893-901.

Presentation of a case of diabetes insipidus in a man of 20 years with a positive blood Wassermann reaction, to whom anti-luetic treatment was given together with pituitrin injections four different times. The diuresis was diminished each time and the molecular concentration showed a parallel rise. Sodium chloride and nitrogen were in general excreted in smaller amounts, although their percentage was increased.—J. A. H.

(DIABETES) Experiments on intermediate carbohydrate metabolism in man. I. (Studien über den intermediären Kohlehydratestoffwechsel. I.). Stepp (W.) & Lange (H.), Deutsch. Arch. f. klin. Med. (Leipzig), 1920, **134**, 47-58.

If the quantity of acetone in the urine is determined and then the urine is heated with oxide of silver and after this the quantity of acetone is again measured, it is found to be less. Since acetone is not itself oxidized by silver oxide this proves that what we call acetone in urine is a mixture of two substances: a substance oxidized by silver oxide together with actual acetone. This substance is volatile, reduces Fehling's solution and gives iodoform with iodine and sodium hydrate. It reduces ammoniacal silver solution. It is certain that this substance is an aldehyde and probably acetaldehyde. It is found in urine only when acetone and diacetic acid are present, and especially when acidosis is becoming more marked.—J. K.

(DIABETES) Experiments on intermediate carbohydrate metabolism in man. II (Studien über den intermediären Kohlehydratsoffwechsel. II.). Stepp (W.) & Zumbusch (H.), Deutsch. Arch. f. klin. Med. (Leipzig), 1920, **134**, 112-118.

Stepp has previously shown that normal blood contains formic acid (Ztschr. f. physiol. Chem. (Berlin), 1920, **109**, 99). In diabetes the amount of formic acid is diminished or entirely absent.—J. K.

Value of the lactone form of glykoheptonic acid in the treatment of DIABETES mellitus (Om vardet af glykoheptonsrelation vid behandlingen af diabetes mellitus). von Wendt (Dora), Finska Läkares. Handl. (Helsingfors), 1916, **58**, 664-675.

A testing of the material named in four cases of diabetes mellitus. The glycosuria was stopped—in one of the cases, however, only during the first day of the treatment. The acidosis was not influenced to a definite degree. The material is of greatest efficacy in mild cases of diabetes, when it quickly makes the patient sugar-free.—J. A. H.

Starvation treatment of DIABETES. Widmark (E.), Allm. sven. Läkaretidn. (Stockholm), 1916, **13**, 1140-1144.

Mainly bibliographical.—J. A. H.

Experiments on carbohydrate metabolism and DIABETES. III. The permeability of blood corpuscles to sugar. Wishart (Mary B.), J. biol. chem. (Baltimore), 1920, **44**, 563-587.

An extensive tabular presentation of experiments on dogs, goats, sheep and a pony, tending to throw light on the question of the permeability of the red-blood corpuscles for sugar. No specific alteration of the distribution of sugar between the plasma and corpuscles was found in experiments with different amounts and modes of glucose administration, different degrees of **pancreatectomy**, and **diabetes**, lipemia, acidosis, exercise, cold, or different levels of the renal threshold.—F. S. H.

Experiments on diminished immunity against purulent infection in patients with DIABETES (Untersuchungen über die verminderte Immunität Zuckerkranker gegen eitrige Infektionen). Wolfsohn, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 986.

The author determined the opsonic index of patients with diabetes. The phagocytic count against staphylococcus in diabetics is distinctly lower than in normal individuals. After infection the number of leucocytes in the blood is lower than in healthy individuals. Vaccine therapy in diabetes is of considerable value in cases of infection.—J. K.

(ENDOCRINE ORGANS) Diseases of ductless glands. Anon., Med. Sc., Abst. & Rev. (London), 1920, **3**, 212-223.

In this article is presented an interesting digest of some of the more recent literature on diseases and therapy of the endocrine organs. The glands treated are the thyroid, parathyroids, suprarenals, hypophysis, and pineal, together with pluriglandular syndromes. Several paragraphs have been quoted as abstracts in this number of Endocrinology.—R. G. H.

(ENDOCRINE THERAPY) L'opothérapy en thérapeutique infantile. Apert (E.), Presse méd. (Paris), 1920, **28**, 341-343.

Apert remarks that except for thyroid treatment in myxedema, very little use is made of organ extracts in pediatrics, and yet this is a particularly fertile field for them. The children's clinics, fetal findings and the results of experimental research all confirm that the suprarenal cortex, like the thyroid, stimulates the nutritional processes. But, with thyroid excessive stimulation, there is emotionalism and a tendency to lose weight, while with suprarenal cortex excessive stimulation, the tendency is to obesity and virilism. Apert advises that organ extract treatment be begun with small doses for three days each week, watching the pulse, the weight and the excitability. With uniform backward growth, he has obtained the best results with a combination of thyroid and suprarenal powder, especi-

ally in the thin, anemic and frail. If the sexual development is precocious, he associates pituitary with the other extracts, with or without suspension of the suprarenal extract. In mongolism, or depressed vitality from any cause, this associated organotherapy often whips up the sluggish development and renders the children easier to teach. He insists that administration by the mouth is as effectual as by subcutaneous injection. The powder can be given with a mouthful of food. Calcium seems to promote the action of thyroid extract, and magnesium that of the suprarenal extract. The indications for pituitary treatment will be found among the short and stout, hairy subjects, with precocious puberty; for suprarenal treatment, among the overtall, weak and apathetic, and among boys, in those with a tendency to feminine characteristics; for thyroid treatment, among those with uniform backward growth, gait, speech and intelligence and delayed development of the sexual organs.—J. Am. M. Ass., **75**, 208.

(ENDOCRINE ORGANS) Increase of agglutinins after organotherapy as a proof of the stimulating action of organ preparations (Erhöhung des Agglutininspiegels durch Organpräparate als Ausdruck leistungssteigernder Wirkungen in der Organotherapie). Borchardt (L.), Therap. Halbmonatsh. (Berlin), 1920, **34**, 536-541.

The author has previously reported that when anti-typhoid inoculations are accompanied by injections of adrenalin or hypophysin the agglutin titre is increased. In this article a similar increase is reported to follow the injection of spermin and of "asthymolysine." Thyroid administered by mouth has a similar influence.—J. K.

A case of multiple sclerosis of the ENDOCRINE ORGANS (Di un caso di sclerosi multipla della glandole endocrine). Bussi (A.), Gazz. d. Osp. (Milano), 1920, **41**, 715-716.

A description of a patient of 50, who first lost his hair and whose **testicles** then became smaller and smaller. His sexual desires diminished and he became sexually impotent. Then he lost his pubic and axillary hair as well as his beard. He always complained of feeling cold; his skin was very dry. The heart beat was slow, the blood pressure was 57, the nails were fragile. **Prostate** and **thyroid** were exceedingly small. The skin and the mucous membrane showed brown pigmentation. From time to time there was polyuria. The patient showed all symptoms of asthenia cordis.—J. K.

(ENDOCRINE ORGANS) A case of pluriglandular sclerosis with clinical picture of Addison's disease (Ein Fall von multipler Blutdrüsensklerose unter dem klinischen Bilde eines Morbus Addisonii). Donath (J.) & Lampl (H.), Wien. klin. Wchnschr., 1920, **33**, 962-964.

A woman of 24, who during childhood suffered from several infectious diseases, became suddenly ill with intestinal symptoms, debility, pigmentation of the skin and mucous membrane of the mouth,

hypertension, loss of pubic hair and cessation of menstruation. The post-mortem showed a small **thyroid** and liver, with marked increase of connective tissue. Symptoms of infantilism (narrow aorta, infantile uterus), were also present. In the **adrenals** the medulla was changed into a mass of connective tissue, while in the cortex there was a chronic inflammation. Sclerosis of the **hypophysis** was also found.—J. K.

(ENDOCRINE ORGANS) Pathology and therapy of the so-called "constitutional adiposity" (Pathologie und Therapie der sog. "Konstitutionellen" Fettsucht). Grafe (E.), Deutsch. Arch. f. klin. Med. (Leipsig), 1920, **133**, 41-63.

A careful study of the metabolism of ten cases of adiposity. Two cases were due to a **thyroid** disturbance, three to **ovarian** insufficiency, and two were of **hypophysial** origin. The three other cases did not show any special endocrine abnormalities. Only in one case of thyroid adiposity, in one case of dystrophia adiposo-genitalis and in one without endocrine disturbance was there a lowered metabolism. In the other seven cases the metabolism was normal. It is probably not true that adiposity is caused by a defective oxidation of fat. It is well known that patients with adiposity retain much water in the tissues. The studies of Eppinger have shown that thyroid preparations are excellent diuretic drugs in edema. This may be one of the reasons why thyroid therapy is indicated in adiposity.—J. K.

(ENDOCRINE ORGANS) A case of dystrophia myotonica (Beobachtungen an einen Fall von Dystrophia myotonica). Mau (O.) & Zondek (H.), Berl. klin., Wchnschr., 1920, **57**, 788-789.

A report of the case of a patient who had an enormous nose, large lips and polyuria. These symptoms may be attributed to a disturbed function of the **hypophysis.** The low blood pressure and the extremely low amount of blood sugar (0.04%) may be caused by **adrenal** insufficiency. The protein metabolism was retarded and the nitrogen excretion was very slight as it is in **myxedema.** The electrocardiogram showed an extra long A. V. interval.—J. K.

ENDOCRINE GLANDS and syphilis (Syphilis e glandulas endocrinicas). Nonohay (U.), Arch. Rio Grand. de med. (Porto Alegre, Brazil), 1920, **1**, ——, (May).

The author proposes a conception which in his judgment revolutionizes the ideas concerning syphilis. He thinks that the disorders of syphilis of the adult and particularly all hereditary phenomena are due to the selective attack of the treponema on the endocrine glands, the functions of which are accordingly destroyed.—B. A. H.

(ENDOCRINE ORGANS) A case of idiocy with marked adiposity (Intorno ad un caso di idiozia con notevole obesità). Pedercini (E.), Morgagni (Milano), 1920, **62**, 253-264.

A description of a woman of 25, weighing 95 kilos. Menstruation began at 15, but was always irregular. She suffered from epilepsy and had mental disturbances (attempted suicide, smeared with feces, etc.). The temperature was sub-normal. Her face was cretinous. The author believed that this disease is caused by endocrine disturbances. He tried **thyroid** and **hypophysis** medication. This had a remarkable effect; the weight was rapidly diminished and the number of epileptic attacks was markedly reduced.—J. K.

Physiological action of different extracts of ENDOCRINE ORGANS in myxedema [De l'action physiologique de différents extraits de glandes à sécrétion interne chez les myxoedémateux (application au diagnostic de l'insuffisance thyroïdienne fruste)]. Porak (R.), Ann. de méd. (Paris), 1920, **6**, 469-476.

Porak has found that injection of thyroid extract in myxedema does not have a definite physiological effect, whereas in normal subjects it causes hypotension and acceleration of the pulse. In two myxedematous patients, who were still under the influence of treatment, there was a suggestion of physiological reaction, which was completely abolished when the treatment was discontinued for a longer period. He also found that adrenalin and extract of the suprarenal medulla had a more powerful action in normal subjects than in myxedema. On the other hand, extract of the posterior lobe of the hypophysis had a much more active effect on the blood pressure of myxedematous patients than of normal subjects, as was shown by a sudden and prolonged fall of blood pressure. By application of these glandular tests to various complex syndromes, Porak shows that it is possible to confirm or exclude the diagnosis of thyroid insufficiency.—Med. Sc. Abst. & Rev., **3**, 216.

(ENDOCRINE ORGANS) The biochemistry of the adrenals, thyroid and hypophysis (Zur Biochemie der Nebenniere, Thyreoidea und Hypophysis). Richter, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 954-955.

According to the author, the **chromaphil system**, the **thyroid**, and the **hypophysis**, together, form a reducing system with the function of producing reducing substances. Diabetes is due to a hyper-function of this reducing, or a hypo-function of the oxidative system. It is possible to prepare the reducing substance from the organs and the blood. They should have an influence on the coagulation of the blood, on the quantity of calcium in the bones, etc. The oxidative system comprises the lymphatic system. The **thymus** has an "antagonistich-komplementierende" relation to the thyroid. The vagus is the nerve of oxidation, the sympathetic that of reduction. (See also Endocrinology, 1919, **3**, 533.—J. K.

(ENDOCRINE ORGANS) Dwarfism (Ueber Zwergwuchs). Sternberg (C.), Wien. klin. Wchnschr., 1920, **33**, 764.

Of no immediate endocrine interest.—J. K.

(ENDOCRINE ORGANS) A quantitative method for the determination of vitamine in connection with determinations of vitamine in glandular and other tissues. Swoboda (Frederick K.), J. biol. chem. (Baltimore), 1920, **44**, 531-551.

Having developed William's biological test for the detection of small amounts of water-soluble-B vitamine, the method was applied to various organs and tissues. A table is given of the so-called vitamine number of the organs studied and it is evident that this specific vitamine is present in large amounts in most of the glands of internal secretion which are of developmental importance, while it is generally low in the other organs examined, with the exception of the liver and kidney. Tissues high in nuclear material such as the **thymus** and lymph glands, were low in vitamine content. Fresh **pancreas** is also low. **Thyroid** in high concentration has a toxic effect on the method, but by proper regulation is shown to contain the water-soluble-B. The order of the endocrine glands as expressed in their vitamine number is: **testes, pineal, pars intermedia** of the hypophysis, **hypophysis** as a whole, **anterior lobe** of the hypophysis, **thyroid, adrenals, ovaries, thymus, posterior lobe** of the hypophysis, **pancreas.**

—F. S. H.

(ENDOCRINE ORGANS) The influence of the several parts of the human body on each other (Over den invloed van verschillende deelen van het menschelijk lichaam op elkaar). de Vries Reilingh (D.), Geneesk. Blad. (Haarlem), 1920, **22**, 161-178.

A good general review of the correlation of the endocrine glands.

—J. K.

The heart in diseases of the ENDOCRINE ORGANS (Herzbefunde bei endokrinen Erkrankungen). Zondek (H.), München. med. Wchnschr., 1920, **67**, 793; Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1239-1240.

In **acromegaly** tachycardia is observed, with a decided inclination towards arteriosclerosis. Very often there exist cardiac insufficiency and, especially in cases without gigantism, dilation of the heart. In chondrodystrophy the heart is enlarged (probably dilated) and the blood pressure is low. In myotonia there is increased irritability of the heart with brachycardia, dilation, and low blood pressure. In the electrocardiogram the period between the atrial wave and ventricular interval is longer than normal. In myxedema there is often cyanosis combined with dilation of the heart. The electrocardiogram is remarkably flat, as many individual waves are lacking. When **thyreojodin** is given, the electrocardiogram resumes its normal outline.

As "formes frustes" of myxedema are very frequent, in cases in which digitalis gives no results thyreojodin should be given a careful trial. —J. K.

(GONADS) Contribution to the physiology of the glands. 43. Studies of the respiratory metabolism of castrated rabbits (Beiträge zur Physiologie der Drüsen. Leon Asher. 43. Untersuchungen über den respiratorischen Stoffwechsel kastrierter Kaninchen). Bertschi (H.), Biochem. Ztschr. (Berlin), 1920, **106**, 37-55.

Using Haldane's apparatus to determine the respiratory exchange B. was unable to detect any changes from the normal in rabbits from which the ovaries or the testes had been removed. Moreover, the injection of freshly made ovarian extracts or of testicular extracts into the animals, whether normal, castrated or spayed, had no evident effect on the respiratory exchange. Consequently, there is at present no direct evidence that the gonads exert any influence of a direct nature upon respiratory metabolism.—F. S. H.

(GONADS) Steinach's operation on man (Steinachsche Tierversuche auf die Menschen übertragen). Lichtenstein, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1211.

Data reported elsewhere.—J. K.

(GONADS) Steinach's studies on rejuvenation (Zu den Steinachschen Verjüngungsversuchen). Liek (E.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1167-1168.

In general the work of Steinach is commended. The author, however, does not believe that mere ligation of the vas deferens or Roentgen radiation of the gonads will bring about rejuvenation. Both these procedures have been repeatedly carried out for other purposes in clinical practice, but it has never been observed that patients get younger. The cases cited by Steinach prove merely that in sexual matters suggestion plays an important role.—J. K.

Studies on the GONADS of the fowl. I. Hematopoietic processes in the gonads of embryos and mature birds. Nonidez (J. F.). Am. J. Anat. (Phila.), 1920, **28**, 81-113.

The connective tissue of the gonads of the fowl is found at times to contain centres of hematopoietic activity. Certain of these blood- and lymph-forming cells, according to Nonidez, have been termed interstitial cells and an endocrine function ascribed to them. Such, he believes, are the granule-laden cells described by Boring and Pearl.—W. J. A.

(GONADS) Treatment of large malignant growths of the male and female generative organs with x-rays (Behandeling der uitgebreide

kwaadaardige gezwellen van de mannelijke en vrouwelijte geslachtsklieren met Röntgenstralen). Orbaan (C.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, **64** (II), 787-796.

Of no immediate endocrine interest.—J. K.

(GONADS) The experiments of Steinach on rejuvenation (Steinach's Verjüngungsversuche). Romeis (B.), München. med. Wchnschr. 1920, **67**, 1020-1021.

Steinach has described experiments on old rats in which ligation of the funiculus spermaticus (on both sides) caused a marked increase in vitality. Lichenstein operated in the same way on three elderly men and, so he states, with success. The author discusses the experiments of both of these investigators and reaches the conclusion that no great confidence can be placed in the efficacy of these operations. The time for observation, especially in men, is too short. Some years ago resection of the funiculi spermatici was frequently done for hypertrophy of the prostate, and it is a noteworthy fact that in none of the cases was there any indication of rejuvenation of the patient. Romeis himself saw a patient in whom the sexual desires returned after a simple operation for hydrocele. Great caution is needed in the interpretation of such an experiment..—J. K.

(GONADS) The skeleton in hermaphroditism (Das Skelett eines Teilzwitters). Stieve (H.), Arch. f. Entwckslngsmech. d. Organ., 1920, **46**, 38-84.

Stieve points out that Steinach's views on hermaphroditism hold, if proof is obtained that the formation of germ cells is dependent upon interstitial cells. He describes a case of scrotal hypospadia associated with anus praeternaturalis scrotalis, in which examination of the generative glands showed that it was completely male. On the basis of the skeletal measurements, which are given, it was decided that the case was one of partial hermaphroditism. Ber. ü d. ges. Physiol., **1**, 24.

(GONADS) The practical value of Steinach's operations (Die praktischen Aussichten der Steinachschen Verfahrens). Stutzin (J. J.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 966.

The author points out that it is difficult to obtain testicles for transplantation. We have no right to take them from healthy individuals, and cases of cryptorchism in which a testicle has to be removed, are rare. It would be better never to perform castration except in cases of malignant tumors. In nearly all cases of tuberculosis it is necessary to remove the epididymis only. The results in homosexuality may be due to suggestion, and even if this were not true, it is impossible to foretell which cases would be suitable for this treatment. The operation of ligating the vas deferens for the

purpose of restoring youth is to be regarded with suspicion, as during many years this procedure has been followed in hypertrophy of the prostate without ever having given rise to rejuvenation of the patient. Until we know more about the matter, surgeons should not resort to these operations.—J. K.

X-ray treatment of the HYPOPHYSIS in bronchial asthma (Irradiazione dell ipofisi nell' asma bronchiale). Ascoli (M.) & Fagiuoli (A.), Gazz. Osp. (Milano), 1920, **41**, 696.

The authors tried to find out whether it was possible to stimulate the endocrine glands with x-rays. First they tried x-ray treatment of the **hypophysis** in a case of dystrophia adiposo-genitalis, and of the **thyroid** and hypophysis in a case of scleroderma with success. Then then treated five patients with bronchial asthma exposing the hypophysis to small doses of x-ray with good results. The authors suggest the study of the function of the endocrine glands by submitting them to small stimulating doses of x-rays.—J. K.

Case of tumor of HYPOPHYSIS, acromegaly and bitemporal hemianopsia. Behse (Emil), Finska Läkares. Handl. (Helsingfors), 1920, **62**, 382-395.

The case is reported of a 47-year-old carpenter who, in his youth, had suffered from recurrent attacks of severe headaches four or five times a year. For the past fifteen years there has been a gradual overgrowth of different parts of his body, especially the hands and feet. Impairment of vision also occurred. For two years tiredness and somnolency have been general, accompanied by profuse sweating and severe thirst, as well as heat sensations in the extremities and acroparesthesia in the finger and toe tips. Potency and libido sexualis were completely lost. Diabetes mellitus, exopthalmus, sluggish pupillary reaction, almost complete amaurosis of the left side, right temporal hemianopsia (V:6-15) and bilateral optic atrophy were present. Enlargement of the sella turcica was evident. Treatment first with **thyroidin** tablets and potassium iodide, then with hypophysis tablets (Merck) 3-10, was initiated. During the two and a half months' period of observation there was a continued improvement of the eye symptoms.—J. A. H.

Products from the HYPOPHYSIS gland. Flaecher (F.) & Reuter (B.), U. S. patent 1,296,063, March 4th, 1919.

The well ground infundibular portion of the hypophysis is extracted with slightly acidulated water and the extract so obtained is freed from albumin and concentrated by evaporation. The concentrated extract is acidulated with sulfuric acid and then treated with an aqueous solution of phosphotungstic acid as long as a precipitate is produced. The precipitate thus formed is washed with water, acidi-

fied with sulfuric acid and then stirred into a thin magma with water and treated with barium hydroxide until a distinct alkaline reaction is produced. The barium phosphotungstate thus formed is filtered off, the filtrate is freed from dissolved barium by the addition of dilute sulfuric acid and then evaporated in vacuo to the point of crystallization; or the base may be precipitated by the addition of alcohol or acetone and washed and dried in vacuo. The base thus obtained is soluble in water with an alkaline reaction, is difficultly soluble in alcohol, ether, ethylacetate and acetone; it is soluble in alkalies and acids. It is stable in air. With acids the base forms crystalline salts, which, like the base itself, possess the physiological properties of the hypophysis and may be used for hemostatic, astringent, pressor or oxytocic effect. The compound is precipitated by alkaloidal reagents such as picric acid, tannic acid, phosphotungstic acid, bichloride of mercury, mercury potassium iodide, potassium periodide, platinic chloride, or potassium bismuth iodide. It gives the biuret reaction and does not yield, on addition of iron chloride, the green coloration characteristic of **adrenalin.** U. S. patient 1,296,064 relates to the manufacture of the salts of the base. The sulfate is formed by combination of the base with sulfuric acid in aqueous solution and concentrating the solution in vacuo until crystallization is effected. It is slightly yellowish, stable, crystalline powder which decomposes at 160 to 161°. It is readily soluble in water and difficultly soluble in alcohol, ether, ethyl acetate and acetone. The base also forms salts with the following acids: hydrochloric, nitric, boric, succinic, oxalic, citric, tartaric, benzoic and salicylic acids. Chem. Absts. 13, 1517.—F. S. H.

(HYPOPHYSIS) Recklinghausen's disease with acromegaly (Coexistencia da doenca de Recklinghausen com acromegalia). Castro (A. de), Rio de Janiero, 1920. F. Briguiet, ed.

Castro, in 1912, reported a case of co-existing cutaneous neurofibromatosis and acromegaly (N. icon. Salpêtriére). In 1915 the case came to autopsy. A tumor of the hypophysis was found. Histological examination was not made.—B. A. H.

(HYPOPHYSIS) Acromegalia e tabes. Notes e observaçoes clinicas. Castro (A. de), Rio de Janiero, 1920, F. Bruguiet, ed.

The author reports the simultaneous occurrence of acromegaly and tabes in a patient.—B. A. H.

(HYPOPHYSIS) Syndroma Thyreo-Hypophysaria. Notes e observaçoes clinicas. Castro (A. de), Rio de Janiero, 1920, F. Bruguiet, ed.

In 1912 Castro reported a case (Encephale, 1912, 329) as **thyrotesticulo-hypophyseal** syndrome. More recently he has concluded that the testicle did not figure etiologically and that the patient had typical acromegaly with slight goiter.—B. A. H.

(HYPOPHYSIS) Distortions of the visual fields in cases of pituitary tumors. Josephson (Arnold), Nord. med. arkiv. (Stockholm), 1616, F. 3. 16. Afd. 2. 1-5.

A claim for priority since the author in 1903 distinctly showed in his work on acromegaly and pituitary tumors the distortions of the visual field in case of pituitary tumors described in 1905 by Cushing and Walker in BRAIN.—J. A. H.

(HYPOPHYSIS) The cause of diabetes insipidus (Zum Wesen des Diabetes insipidus). Hecht (E.), Ztschr. f. klin. Med. (Berlin), 1920, 90, 126-145.

A man contracted syphilis and was treated with inunctions of mercury until a negative Wassermann reaction was obtained. Some years later, after a single injection of salvarsan, diabetes insipidus immediately appeared, and gradually the condition of dystrophia adiposo-genitalis developed. Further treatment with salvarsan had no effect. The skiagram revealed no abnormality of the sella. From his observations on this patient the author is led to conclude that in diabetes insipidus the diuresis is due merely to increased permeability of the kidney to water. Veil's contention that the anti-diuretic effect of pituitary extract is due to the retention of water by the tissues is controverted. Although, when extra amounts of NaCl are administered, the elimination of this is brought about by an increase in the quantity of urine, it is also true that the concentration of NaCl in the urine is higher than when an equal degree of diuresis is produced by the ingestion of water. It follows, then, that the concentrating power of the kidney still exists. In fever, during thirst, or after injections of pituitary extracts, in diabetes insipidus, the concentration of the urine may be increased, although it does not reach the normal. Often the polyuria of diabetes insipidus is considered as a simple compensatory mechanism for the loss of concentrating power of the kidneys. That such is not the case is indicated by the fact that in true compensation polyuria the epithelial cells of the renal tubuli are found to be flattened, whereas this is not true in diabetes insipidus. It is not possible to consider polyuria as compensatory when the concentration of the urine is lower than that of the blood plasma.—J. K.

(HYPOPHYSIS) Diagnosis of hypophyseal asthenia (Zur Diagnose der Hypophysenschwäche). Fliess (W.), Med. Klin. (Berlin), 1920, 16, 778-781.

Fliess describes a syndrome characteristic of insufficiency of the anterior lobe of the hypophysis and consisting of five principal manifestions, viz., (1) general fatigue; (2) lack of power of concentration; (3) polyuria, occasionally accompanied by enuresis; (4) occipital neuralgia, not infrequently accompanied by a backache and sciatica;

(5) disturbances of menstruation, especially menorrhagia. The first four symptoms, though most frequent in women, especially during pregnancy, may also be found in the male sex at puberty. All the symptoms may be caused to disappear by administration of tablets made from the anterior lobe. Fliess emphasizes the importance of examining all the other members of the family to which the patient belongs for similar disturbances.—Med. Sc. Abst. & Rev., **3**, 219.

(HYPOPHYSIS) Late acromegaly (Acromegalie à début tardif). Hamant (A.) and Caussade (L.), Rev. méd. de l'est., 1920, **48**, 446-448.

Acromegaly of late onset is exceptional. Examples of the kind have been recorded by Widal, Ballet and Laignel-Lavastine, to which may be added the case recently reported by Hamant and Caussade. The patient was a woman, aged 53, the mother of three children, in whom the first symptoms, enlargement of the hands and feet, had appeared at the menopause four or five years previously. Subsequently the skin of the face and neck grew thick. Deformities of the trunk, visceral signs, and symptoms of compression were absent, but the diagnosis of acromegaly was confirmed by the x-rays, which showed enlargment of the sella turcica.—Med. Sc. Abst. & Rev., **3**, 218.

(HYPOPHYSIS) A case of suspected tumor of the pituitary body. Hansell (H. F.), Ophth. Rec. (Chicago), 1917, **26**, 275-278.

A case is recorded presenting interesting eye findings, dilatation of the pupils, concentric contraction of the right field and complete left hemianopsia. The x-ray plate of the skull suggested a tumor in the region of the sella turcica. Neurological examination revealed nothing abnormal. There were no indications of acromegaly. The eye grounds were normal. The headache and vomiting seemed to be relieved by **pituitrin** and **thyroid** extract.—H. L.

(HYPOPHYSIS) Exhibition of a case of gigantism in a girl 12 years of age. Heuer (G. J.), John Hopkins Hosp. Bull. (Balt.), 1917, **28**, 96.

Heuer presented before the Johns Hopkins Medical Society, Oct. 16, 1916, a girl of 12, whose height was 6 feet 1 inch and whose weight was 117.5 lbs. The extremities were abnormally long and the hands and feet very large, but not acromegalic. There was a beginning bitemporal hemianopsia. The x-ray plate of the skull showed an enlarged sella turcica with atrophy of the posterior clinoid processes. There were no signs of **thyroid** disturbance, **adrenal** disease, or **pineal** involvement. No gynecological examination was made. Menstruation had not begun. The response to adrenalin and atropin were normal, as was the blood sugar curve.—H. L.

The histological structure of the HYPOPHYSIS and hypophyseal adenomas together with their relation to acromegaly. Kalmeter (Gunnar), Hygiea (Stockholm), 1916, **78**, 609-627.

A single case of hypophyseal tumor without acromegaly is reported. The tumor was shown to be a so-called chief-cell adenoma. The individual cells agreed completely with the "chromophobic" chief cells of the normal hypophysis; acidophile cell granules could not be found at any place. Cell polymorphism and other evidence of malignancy were lacking. The finding gives rise to the opinion that the acidophile granules are the effective secretion product of the hypophysis and that an overproduction of such secretion leads to acromegaly.—J. A. H.

(HYPOPHYSIS) Dystrophia adiposo-genitalis. Hoffmann. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1266.

A demonstration of a boy of eleven with this disease and a "forme fruste" of Recklinghausen's disease (general neurofibromatosis). There was a bilateral atrophy of the optic nerve which may have been caused by a neurofibroma of the chiasma.—J. K.

(HYPOPHYSIS) Relation between diabetes insipidus and disturbances of hypophyseal functions. af Klercker (Kj. Otto), Allm. sven. Läkartidn. (Stockholm), 1916, **13**, 909-918.

After a review of the literature on the question the author comes to the conclusion that one is not justified in considering as satisfactory the theory of hypophyseal genesis of diabetes insipidus. The not infrequent association of this disorder not only with acromegaly but also with the still rather uncertain dystrophia adiposo-genitalis, is not conclusive. In the last analysis the question reduces to a "non liquet."—J. A. H.

(HYPOPHYSIS) Acromegaly. Kraus (E. J.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 932.

At the autopsy of a patient dying with acromegaly there was found a large eosinophile adenoma of the hypophysis. The heart weighed 950 grams, the liver 3220 grams, the spleen 650 grams, the **thyroid** 150 grams, the **pancreas** 150 grams, and the **adrenals** 25 grams. **Pineal, parathyroids** and **testicles** were of normal weight.—J. K.

Tumors of the HYPOPHYSIS (Hypophysisgezwellen). Kuijjer (J. H.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, **64**, 1971-1979.

A report of five cases treated with x-rays:

1. A man of 23, with headache, vomiting, giddiness, almost complete blindness and adiposo-genitalis. After x-ray treatment the headache was slightly less intense. He died a year later. No post-mortem was held.

2. A woman of 52, with headache, disturbances of speech, and almost complete blindness. After treatment all symptoms disappeared. The sight was very much improved.

3. A woman of 49, who was tired, giddy and nearly blind, the right eye being completely so. After treatment she was much improved. The sight became better.

4. A woman of 40, with pains in arms and legs, headache, poor vision, amenorrhea and symptoms of dystrophia adiposo-genitalis. After treatment there were no complaints and the vision was perfectly normal.

5. A man of 26 had headache, bad sight and protrusion of the left eye. He was sexually impotent. After treatment there was no complaint; the protrusion disappeared. He remained impotent.

In all these cases the diagnosis of hypophyseal disturbance was absolutely sure. The improvement in the last four cases has lasted now for over two years.—J. K.

(HYPOPHYSIS) A case of symmetrical lipodystrophy (Ein Fall von symmetrischem Fettschwund). Mosse, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 985.

A short note. The respiratory quotient was normal. The blood showed only a relative lymphocytosis. The hypophysis was normal. About twenty-five such cases have been reported in the literature. The etiology is unknown.—J. K.

(HYPOPHYSIS) Dystrophia adiposogenitalis (Zur Dystrophie adiposogenitalis). Pfeiffer (R.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1302.

The patient was a girl of 17 with dystrophia adiposo-genitalis and polyuria. The x-ray pictures showed an enlarged sella turcica. Death occurred 48 hours after operation. Autopsy showed the ependyma of the third ventricle partly changed into a number of layers of epithelium with the formation of a solid benign tumor in the infundibulum, consisting of layers of epithelial pearls (so-called Hypophysengangsgeschwülst of Erdheim). The pars intermedia and the anterior lobe of the hypophysis were normal.—J. K.

HYPOPHYSIS and Raynaud's disease (Hypophyse und Raynaudsche Krankheit). Pribram (B. O.), München med. Wchnschr., 1920, **67**, 1284-1286.

A man of 42 developed Raynaud's disease. There was no loss of nails but a gradual loss of teeth; no ocular symptoms or acromegaly. There was obstruction of the nose. When the skin was examined it was seen that the blood in the capillaries intermittently ceased circulating for a short time. This symptom was due to local angiospasms. There were also symptoms of latent tetany (Chvostek's symptom was

positive). The x-ray pictures showed an enlarged sella. Hypophysis preparations met with marked success, and it was therefore deemed probable that hypophysis extract exerts a regulating influence upon blood-vessel tone. In Raynaud's disease periods of achylia gastrica are observed. The author supposes that these periods are due to vasomotor disturbances in the stomach.—J. K.

(HYPOPHYSIS) Hypophyseal cachexia (Hypophysäre Kachexie). Reye, München. med. Wchnschr., 1920, **67**, 1302.

A short note on a patient with syphilis and hypophyseal cachexia. Treatment with mercury, salvarsan and asthmolysin was followed by improvement. The patient became less dull and the pubic hair and eyebrows, which had previously been lost, began to grow again. —J. K.

(HYPOPHYSIS) Tumors of squamous epithelium of the infundibulum, their structure and position in the oncological system (Plattenepithelgeschwülste des Infundibulums, ihr Bau und ihre Stellung im onkologischen System). Siegmund, München. med. Wchnschr., 1920, **67**, 827.

The author examined four of these tumors, which were originally described by Erdheim. Their structure is complicated. They always contain cysts. The epithelium resembles in its morphology that of the tissue from which the enamel of the teeth is derived. The stroma of the tumor consists of connective and glial tissue. Masses of necrotic columnar epithelial cells, surrounded by giant cells, and often containing a large quantity of calcium, are characteristic. In three out of four cases the tumors were invasive; in two cases, clinically resembling dystrophia genitalis, the hypophysis was unchanged. The tumors are not teratomata, but probably originate from the ectoderm of the buccal cavity, from rests of the fetal ductus hypophysis. In two of the cases dystrophia genitalis without adiposity occurred. It is possible that the adiposity in such cases is not related to the hypophysis, but is secondary to the atrophy of the **gonads**.—J. K.

A case of tumor of the HYPOPHYSIS (Een geval van hypophysegezwel). de Stella (H.), Vlaanischgeneesk. Tijdschrift (Ghent), 1920, **1**, 440-449.

A report of a case of a boy of 19, who complained of severe headaches and vomiting. After a month the pain disappeared, but the boy gradually became very fat and blind. There was but little hair in the axillae and on the pubes. The testicles were atrophied. Goitre, exophthalmos and tachycardia were present. The x-ray showed an enlarged sella turcica. The patient was first treated with **thyroid** with good result. The adiposity disappeared and the general health improved. **Hypophysis** preparations gave still better results. The

exophthalmus nearly disappeared, but the sight did not improve. Nevertheless, the tumor gradually became larger, organotherapy ceased to be successful and the adiposity again returned. X-ray treatment will be initiated and if this fails, operation will be attempted.—J. K.

(HYPOPHYSIS, THYROID) A case of diabetes insipidus changed to myxedema (Uebergang eines Falles von Diabetes insipidus in Myxödem). Strausz (L.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 939.

An intelligent boy of 9 years developed polyuria (seven liters daily) and polydipsia. When he was 13 these symptoms had disappeared, but he became dull and very stupid. When he was 15 he had typical myxedema, but no symptoms of diabetes insipidus. The patient died of pneumonia when he was 20. No autopsy was performed.—J. K.

(HYPOPHYSIS) (Technik der Hypophysealoperation). Tiefenthal, München. med. Wchnschr., 1920, **67**, 794.

Of technical surgical interest.—J. K.

(HYPOPHYSIS) Extract titration by the isolated uterus method (Titrierung von Hypophysenextrakten am ausgeschnittenen Uterus). Trendelenburg (P.) & Borgmann (E.), Biochem. Ztschr. (Berlin), 1920, **106**, 239-253.

This paper is a report of a study of the assay of some 20 commercial preparations of the extract of the posterior lobe of the pituitary as compared with extracts made by the authors from fresh glands. They found that adult virgin guinea pigs weighing no less than 200 nor more than 250 grams are the animals most suited for the work. Using such animals it was found that while the freshly prepared posterior lobe extracts had an average titer of 0.17 gram β-imidazolylethylamine, the commercial extracts were very much weaker and equivalent to but 0.00025 to .008 grams per 1 gram posterior lobe, as a basis of calculation.—F. S. H.

(INTERNAL SECRETIONS) Paracer a respeito. Barbosa (Renato), Arch. Rio Grand. de med. (Porto Alegre, Brazil), 1920, **1**, ——, (May).

Polemical, concerning a previous report.—B. A. H.

Influence of the glands of INTERNAL SECRETIONS on gastro-intestinal pathology (Influencia das glandulas de secreçao interna na pathologia gastro-intestinal). Dias (Annes), Arch. Rio Grand. de med. (Porto Alegre, Brazil), 1920, **1**, —— (May).

Enthusiastic exposition of the importance of endocrine disturbances in diseases of the gastro-intestinal tract.—B. A. H.

Polycythemia as a hereditary disorder of the INTERNAL SECRETIONS (Ueber Polyzythämie als vererbbare Störung der inneren Sekretion). Engelking (E.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1140-1142.

The author reports the study of a family manifesting polycythemia for three generations. The condition was observed in the grandmother, the mother, and five children. The characteristic age of the appearance of polycythemia is from the 35th to the 55th years. In the family studied, however, the grandmother had died at 24, and one of the children developed the condition at 5. All the children of the family are infantile. The older children showed symptoms of endocrine abnormalities. A daughter of 19, as well as the mother, began menstruation very late, and this function was always irregular. The second child, a girl of 15, has not yet menstruated. Some members of the family were goitrous. The author discusses the question as to whether the formation of red corpuscles is under the influence of the internal secretions. In this connection he cites the observations of Bertelli, Falta, and Schweeger, that in dogs subcutaneous or intravenous injections of adrenalin resulted in an enormous increase in the number of corpuscles (40 to 100 per cent). This influence of adrenalin and other hormones on the blood has been repeatedly confirmed. On these grounds the author believes that hereditary endocrine perturbations may be responsible for polycythemia.—J. K.

INTERNAL SECRETIONS (Innere Sekretion). Kestner (O.), Ztschr. f. ärztl. Fortbild. (Jena), 1920, **17**, 573-581.

A general review. The author states that all endocrine glands are closely related. The most intimate relation exists between the **hypophysis** and the **thyroid**. Growth depends upon the hypophysis and is completed at puberty; therefore most women are smaller than men because puberty in women begins earlier; and the men in southern countries are generally smaller than those in northern regions.

—J. K.

On the cause of the hypertrophy of the surviving OVARY after semispaying (albino rat) and on the number of ova in it. Arai (H.), Am. J. Anat. (Phila.), 1920, **28**, 59-79.

After semispaying in the young albino rat the compensatory hypertrophy of the remaining ovary occurs independently of copulation or pregnancy. The hypertrophy is produced by a greater abundance of well developed normal and degenerate follicles, and by an excess of corpora lutea. The number of ova is only slightly decreased. Semispaying neither hastens nor delays the appearance of the first ovulation.—W. J. A.

The specific hormone of the OVARY (Ueber das spezifische Overialsekret). Fellner (O. O.), Zentralbl. f. Gyn. (Leipzig), 1920, **44**, 1133-1138.

Esch (Zentralbl. f. Gyn., 1920, **44**, 561) has stated that no hormone of the ovary is known. According to the author, this is not true, for he considers the "sexual-lipoid," which he prepared years ago, as the specific hormone. It can be prepared from placenta, "Eihäute," corpus luteum, the interstitial cells of the ovary and the testicle, but from no other organs. When injected into female animals it causes hypertrophy of the uterus, the vagina, and the mammae. In the male animal it causes an enlargement of the breasts. It is not identical with the lipamin described by other investigators, for lipamin causes hemorrhage when injected; sexual-lipoid does not. Lipamin is a mixture of substances; perhaps there are traces of sexual-lipoid in it. The corpus luteum has no relation to bleeding in menstruation, for this may be observed now and then after double ovariectomy. The function of the sexual-lipoid is to prepare the mucous membrane of the uterus for menstruation. In an alcohol-ether extract of ovary and placenta poisonous substances may be found. Therefore, one should use only the author's sexual-lipoid.—J. K.

(OVARY) The treatment of the symptoms caused by a loss of ovarian function with the organo-preparation "Ovobrol" (Die Behandlung der ovariellen Ausfallserscheinungen unter Anwendung des sedativen Organpräprarates "Ovobrol"). Guttmann (E.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1255-1256.

A recommendation of "ovobrol," one tablet of which contains one cc. of ovoglandol and one gram of sodium bromide with some aromatic plant extracts.—J. K.

The influence of iodine on the OVARY (Ueber die Einwirkung von Jod auf die Ovarien). Jastram (M.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1920, **32**, 460-466.

Tiersch has asserted that large doses of iodine have an unfavorable influence on the ovaries of young persons. Jastram has tried to confirm this experimentally. He gave potassium iodide to young dogs of 4, 6 and 7 weeks (up to three grams daily). He observed growth of connective tissue in the ovary, but even after very large doses no changes in the follicular elements could be found. Nevertheless, the author advises care in the use of iodine in young women. —J. K.

MYOTONIA combined with dystrophy (Myotonie in Kombination mit Dystrophie). Rülf, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1178.

The most common symptoms in this disorder are, according to Rülf, dystrophy of the muscles, cataract, testicular atrophy with sex-

ual impotence, loss of hair, and dermographia. The disease is in all probability a pluriglandular endocrine disorder.—J. K.

(PANCREAS) Cytological studies of Langerhans' islets, with special reference to the problem of their relation to the pancreatic acinus tissue. Saguchi (S.), Am. J. Anat. (Phila.), 1920, **28**, 1-57.

A detailed study of the frog's pancreatic islets by means of the more recent cytological methods is reported. Three types of granular and two of non-granular cells are described. The cells of the islets are derived according to Saguchi from the acini.—W. J. A.

PINEAL tumor (Epiphysentumor). Frank, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 900; Wiener klin. Wchnschr., 1920, **33**, 743.

A man 20 years of age died with symptoms of brain tumor. At autopsy a teratoma of the pineal gland was found. The tumor included intestinal tissue, alveoli of lung, connective tissue, muscle, cartilage, epithelium, and neuroglia. In addition, a relatively large amount of pineal tissue remained. It is probably due to this fact that the patient failed to show any symptoms of pineal disease during life.—J. K.

(PARATHYROIDS) A case of peripheral pressure neuritis in tetany (Ein Fall von peripher Druckneuritis bei Tetanie). Beth (H.), Wien. klin. Wchnschr., 1920, **33**, 701-703.

A patient with pneumonia suddenly developed clonic spasms in both arms with all symptoms of tetany. The spasms continued for four days. On the third day trophic changes were observed in the nails and there was edema of the arms. The spasms gradually subsided but the edema and the Trousseau phenomenon remained; there were ulcers between the fingers and the finger joints were swollen. Gradually these symptoms disappeared but the right hand was weaker than the left and showed atrophy of the small muscles, especially of the thumb and the little finger. The nails of both hands and feet became brittle and after some time the patient lost all of her nails.

—J. K.

(PARATHYROIDS) Tetanie. Elias (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1236.

Report of a patient of 27 with tetany who was successfully treated with intravenous injections of sodium carbonate solution. As it is known that the administration of acid may produce tetanic symptoms, the author believes that acidosis plays an important part in the pathogenesis of tetany.—J. K.

(PARATHYROIDS) Experiments on tetany (Experimentelle Untersuchungen über Tetanie). Farner (E.), & Klinger (R.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1920, **32**, 353-373.

The authors used more than 100 rats in their experiments. The parathyroids were removed and after some time the animals were killed and the **thyroid** and **thymus** examined histologically to see whether or not parathyroid residues remained. Many animals, but not all, within ten to twenty hours after the operation, showed a rigidity, especially of the hind-legs; the fore-legs were bent, and there were tremors of the limbs. These symptoms rarely lasted for more than three hours. The animals developed normally and the sexual functions and pregnancy were also normal. Cachexia as described by other observers was not obtained in these studies. The incisor teeth of the lower jaw always became opaque as has been described by other workers, particularly Erdheim; the teeth often became fragile. Ulcers or necrosis of the bones were not observed. When the animals were frightened they often went into spasms and sometimes died. These symptoms do not depend upon diet, since change of food had no influence. As other authors obtained more typical symptoms, it is possible that different kinds of rats show a different susceptibility to tetany. Farner and Klinger found no differences between wild and tame rats. The technic of the operation had no influence. In animals with and without goiter, the results were the same.—J. K.

Transplantation of PARATHYROIDS in post-operative tetany. Flörcken (H.) & Fritzche (G.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1005-1007.

The patient, a woman of 23, was operated upon 11 years ago for goiter. Three years later she developed attacks of tetany at regular intervals during the cold months. The attacks returned every year at the same time, accompanied by convulsions with loss of consciousness and biting of the tongue; gradually the patient became mentally dull. In 1919, parathyroid tablets were given but without success. (The dosage is not mentioned.) In February, 1920, a piece of **thyroid** and one parathyroid from another patient were transplanted into the musculus obliquus internus.. There was no further recurrence of the spasms after the operation, and the symptoms of Chvostek and Trousseau became much less marked. While it is impossible to call this a positive cure, it cannot be denied that the improvement was important.—J. K.

(PARATHYROIDS) New investigation on the relations between otosclerosis and tetany and on the constitution of patients with otosclerosis (Weitere Untersuchungen über die Beziehung zwischen Otosklerose und Tetanie sowie über die körperliche Konstitution der Otosklerotiker). Frey (H.) & Orzechowski (K.), Wien. klin. Wchnschr., 1920, **33**, 697-700; 734-736; 754-757.

In 1917 the authors published an article in which they proved that patients with otosclerosis often show signs of latent tetany. They now give the history of ten other cases. In five of the patients latent tetany was obvious, in four very probable. In only one patient, not completely examined, were no symptoms of tetany found. These cases nearly always show hypogenitalism (habitus infantilus, obesity, small testicles, few hairs, especially few pubic hairs, short penis, etc.) and symptoms of so-called asthenic constitution.—J. K.

(PARATHYROID) The blood picture in a case of post-operative tetany (Blutbildbeobachtungen bei einem Falle von post-operativer Tetanie). Haas (W.), München. med. Wchnschr., 1920, **67**, 781-783.

In a case of post-operative tetany the author observed a diminution in the number of neutrophylic polymorphonuclear leucocytes, an increase in the number of leucocytes, and some eosinophilic leucocytes. The total number of white corpuscles was diminished during the first few days of the illness but soon became normal again.—J. K.

(PARATHYROIDS) Manifestations of tetany in adults (Manifestazioni di tetania negli adulti). de Paoli (N.), Gazz. d. Osp. (Milano), 1920, **41**, 899.

A short description of four cases. The first is of tetany in a pregnant woman, which was cured after the birth of the child. The second was a patient in whom tetany occurred during lactation. When feeding was discontinued the tetany stopped. The third case is of the occurrence of tetany after influenza. In the fourth there was present a goiter. Classical tetany gradually developed. In this case there was exophthalmos but no tachycardia. The author believes that the goiter had an influence on the parathyroids embedded in the thyroid.—J. K.

A case of tetania gravidarum cured by implantation of PARATHYROIDS (Durch Epithelkörperimplantation geheilter Fall von Tetania gravidarum). Roth (N.), Wien. klin. Wchnschr., 1920, **33**, 886-887.

The subject, a woman of 32, was in her fifth pregnancy, the first four having been normal. She entered the hospital in the sixth month of the pregnancy because of having had various attacks of tetany in the earlier weeks. During these attacks calcium was administered intravenously with temporary benefit. A parathyroid gland obtained from a patient undergoing strumectomy was then implanted. The first three days following the operation no attacks were observed; then three mild attacks occurred. Following these the patient was restored to perfect health and suffered no further symptoms of tetany.—J. K.

PITUITRIN as stimulant to parturition (Ueber die Anwendung minimaler Dosen von Pituitrin zur Einleitung der Geburt am Ende der Schwangerschaft). Stein (A.), Zentralbl. f. Gyn. (Leipzig), 1920, **44**, 1152-1153.

When pituitrin is injected two or three weeks before term it has no effect whatever as a uterine stimulant. During the last days of pregnancy, however, it is possible in about 60 to 70 per cent of the cases to initiate labor by the injection of small doses of pituitrin. The author advises the use of this drug at this time in doses of 0.12 to 0.18 c.c., administered three times at hourly intervals in the muscles of the leg. If ineffective, the procedure may be repeated the next day. Labor so initiated is generally completed within twelve hours. The use of large doses is not advisable.—J. K.

The influence of PITUITRIN on diuresis (Ueber diuresehemmende und diuretische Wirkung des Pituitrins). Brunn (F.), Zentralbl. f. inn. Med. (Leipzig), 1920, **41**, 674-679.

When a given subject ingests a large quantity of water and receives also a hypodermatic injection of 1 c.c. of a 20 per cent extract of hypophysis, the quantity of urine excreted is diminished in the relation of 10 to 1 as compared with excretion following the taking of the same quantity of water without the extract. Similarly, the quantity of NaCl excreted bears the relation of 3 to 1. When, with a given large quantity of water, the subject ingests at different times gradually increasing amounts of NaCl, the quantity of urine gradually diminishes. If, however, pituitrin is injected under these conditions the quantity of urine is increased. This fact was observed in case of normal subjects and of two patients with thyroid disorders. One of these patients had frank Graves' disease and the other a "forme fruste" of the malady. The quantity of NaCl in the blood plasma is not changed when a large amount of water is taken; but when NaCl is ingested it appears in the plasma in increased concentration. This is true whether pituitrin is injected or not. With the refractometer the plasma gives a higher reading after the administration of NaCl and pituitrin than after the NaCl alone. The more dilute is the urine the greater anti-diuretic effect has pituitrin. The author reports some interesting observations upon the isolated kidney of the frog. When hypophysis is injected into the aorta the permeability of the kidney becomes materially less than when the same quantity is injected into the renal vein. Since, in the frog, the blood supply of the glomeruli is from the arteries, while that of the tubuli is from the veins, the observation would indicate that hypophysin acts primarily on the glomeruli.—J. K.

(TESTES) Dystrophia myotonica. Gunther, Deutsche med. Wchnschr., 1920, **46**, 1131.

Case report of a man of 36 with atrophy of the masseters, the sternocleidomastoids, and the muscles of both arms and hands, cataract of both eyes, loss of hair, and marked atrophy of both testicles.—J. K.

(TESTES, THYROID) Dystrophia myotonica. Hauptmann, Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1132.

In this case the symptoms were atrophy of the face, the forearms and the hands, paralysis of the peronei, loss of hair, cataract, increased salivation, very small soft testicles, and goiter. In the blood were found lymphocytosis and eosinophilia—J. K.

(TESTES) Abnormal sexual desires (Abnormer Geschlechtstrieb). Lichtenstern, Wien. med. Wchnschr., 1920, **33,** 893.

The patient was a man of 44 with greatly increased sexual desire. He had symptoms of sadism and suffered from severe headaches. One testicle was removed and successfully implanted into a homosexual. The patient himself, however, was not improved. The second testicle was removed also. All sexual desires then disappeared, as also the sadistic perversion. The second testicle was transplanted into a eunuch with good results.—J. K.

(THYMUS) The modern view of status thymico-lymphaticus and its relation to other diseases (Der jetzige Stand der Lehre vom Status thymico-lymphaticus und seine Beziehung zu anderen Krankheiten). Henke (F.), Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1257-1259.

A general review without new facts.—J. K.

Congenital cataract binocular, complicated by a large persistent THYMUS gland. Tivnen (R. J.), Surg. Clin. Chicago, 1920, **4,** 943-958.

A case report. The patient, 20 months old, was presented for operation. The child was a "blue baby," with the cord once about the neck; resuscitation required two minutes. Weight of child at birth was 6 pounds, 8 ounces; length, 50 cm. For forty-eight hours following birth the child was apparently normal. Early on the third day the nurse found it in a cyanotic condition, with irregular respiration—Cheyne-Stokes in character—and pulse rapid but regular. Examination during this attack disclosed both anterior fontanel and the wide median suture bulging without pulsation; right eyelid edematous, completely closing eye; left eye negative; knee-jerks normal; no contractures or spasms present. For three days following, the baby had almost daily attacks of this character, after which its respiratory and cardiac system gave no further trouble. Two weeks later an oculist made a diagnosis of binocular congenital cataract and recommended deferring operative procedure until the baby was one or more years of age.

The so-called "cyanotic spells" continued at irregular intervals to the twentieth month. The baby never became unconscious; the duration of the attacks was from three to five minutes; slight noises, hunger, fatigue, and undue excitement were the usual exciting factors. A radiogram of the chest disclosed a very large persistent thymus gland. Physical examination disclosed cerebral palsy ascribed to defective glandular secretion and probably also to a cerebral hemorrhage at birth; the chest examination failed to disclose the thymus enlargement. The Wassermann reaction was negative.

The patient was placed on roentgenotherapy at weekly intervals for a period of twelve weeks in order to decrease the size of the gland. A radiogram taken after the last treatment showed practically complete disappearance of the hypertrophied thymus gland shadow. The roentgenotherapy produced a very marked beneficial effect upon the child's general condition. His mentality was greatly stimulated and developed, his vocabulary increased, locomotion, which had previously been absent, was established, and in particular, the "cyanotic spells" were strikingly diminished both as to frequency and severity.

In this patient the clinical history fits perfectly the diagnosis of a large persistent thymus gland. The attacks of dyspnoea, the spells of cyanosis, the delayed development, the mental status, and to some extent the congenital cataracts, are characteristic. In addition the radiogram corroborates the clinical history and the reduction of the hypertrophied gland, as shown by the skiagram, under roentgenotherapy is coincident with the striking improvement in the child's development, mentally and physically and the marked diminution in the severity and frequency of the attacks of dyspnoea.

In connection with the report of this case the author presents a comprehensive review of the anatomy and physiology of the thymus gland. He directs especial attention to the fact that patients with enlargements of the thymus gland are undeniably distinct hazards as candidates for surgical procedures where an anesthetic, local or general, is contemplated, and expresses the opinion that the only safe course to pursue in such cases when an operative procedure is contemplated, particularly in infants and the young and especially when they present lesions attributable to some vagary of evolutionary character is definitely to determine the condition of the thymus gland before the operation is undertaken. In his own practice he has advocated and adopted this plan for some time past as a regular routine of pre-operative investigation. In this connection he refers to the case of an infant of two and a half years, upon whom in the course of several months he was to perform a tonsillectomy and adenectomy, whom the parents one morning found dead in its crib. It had suffered no previous illness of any character and was regarded as in excellent health. Autopsy disclosed a large persistent thymus gland with associated general adenopathy.

In the author's experience, physical examination alone of the chest is neither satisfactory nor conclusive and he has come to regard the x-ray when properly taken by an experienced roentgenologist, as the most reliable and dependable method of investigation. In one of his cases physical examination of the chest by an experienced and skilful diagnostician proved negative, while the x-ray showed a large persistent thymus gland.

Roentgenotherapy is advocated as a satisfactory and useful agent in properly selected cases in reducing the thymus enlargement and improving the general condition and development of the patient. The indiscriminate use of roentgenotherapy, however, is not advisable, particularly in cases where the enlarged thymus has been rendered deficient through focal degenerative changes, with secondary cretinism, myxedema, or Addison's disease. In such cases more harm than good results.—Author's Abst.

(THYROID) The treatment of goiter by the Roentgen ray. Boggs (R. H.), Interstate M. J. (St. Louis), 1917, **24**, 362-367.

Boggs explains the beneficial effect of roentgen rays on hyperthyroidism and malignancy by their power to inhibit proliferation of embryonic cells through their direct action on the nuclei of epithelial cells. He stresses the importance of radiating not only the thyroid, but also the **thymus** and **ovaries** in Graves' disease, pointing out that resection of the thyroid gland does not always cure the disease, because the thymus and ovaries are still over-active. In grave thyroid autointoxication, radiation should be very carefully begun, since stimulation of the gland with increase of symptoms sometimes results at first. The roentgenologist must be careful not to overtreat or myxedema will result. A decrease in pulse rate is the first sign of improvement, usually followed by gain in weight and subsidence of nervous symptoms; reduction of the size of the gland and of the exophthalmos comes later or not at all. The author very briefly reports three typical cases of Graves' disease cured by roentgen rays and remaining well for 7 to 10 years after treatment. Boggs advocates judicious roentgen treatment of the adolescent goiter as a prophylactic measure and has found the patients to be distinctly improved in health even though none of the obvious signs of hyperthyroidism were present.

He also insists that radiation should not be attempted except by an expert familiar with the technic and thoroughly versed in the physiology, pathology and clinical aspects of endocrin disease. Better cosmetic results and lower mortality than can be expected from surgical methods are claimed for the roentgen therapy. [It would be safer if the patient treated with x-rays be systematically watched by an experienced internist and controlled also by basal metabolism studies.]—H. L.

The discovery of the active principle of the THYROID (Ueber die Entdeckung des wirksamen Bestandteiles der Schilddrüse). Widmark (Erik M. P.), Sven. Lärkartidn. (Stockholm), 1920, **17**, 241-246.

Refers to Kendall's research on the composition of "Thyroxin." The point of view is taken that this substance approximates tryptophan in composition and the idea is expressed that tryptophan-poor food should be tried out in cases of hyperthyroidism.—J. A. H.

(THYROID) Contribution to the physiology of the glands. 44. The behavior of normal, thyroid-fed and thyroidless rats to oxygen deficiency (Beiträge zur Physiologie der Drüsen. M. 44. Leon Asher. Das Verhalten von normalen, mit Schilddrüsen-substanz gefütterten und Schilddrüsenlösen Ratten gegen reinen Sauerstoffmangel). Cao (M. D.), Biochem. Ztschr. (Berlin), 1920, **106**, 254-274.

White rats were put under the bell-jar of a vacuum pump and the air partially exhausted. The removed gases were replaced by hydrogen and the behavior of the animals studied. Extensive protocols are appended, the data from which lead to the conclusion that both hypo- and hyper-thyroidism in rats conduces to an increased susceptibility to oxygen deficiency. These facts contribute to an understanding of the behavior of the respiratory metabolism under the influence of pathological conditions of the thyroid.—F. S. H.

Relationship of the THYROID gland to Graves' disease. Crile (G. W.), Can. M. Ass. J. (Toronto), 1917, **7**, 727-731. J. Med. Soc. N. Jersey (Orange), 1917, **14**, 180-182.

Hyperplasia is not a necessary characteristic of Graves' disease, because excision of a sufficient amount of a colloid goiter or of an adenoma in a typical case improves or cures the disease just as it is cured or improved by the excision of a hyperplastic gland. The degree of surgical relief is independent of the histology of the gland. In most pregnant women, in many adolescent girls, in a large proportion of advanced cases of tuberculosis, and in numerous cases of intense pyogenic infection the thyroid is not only hyperplastic but the histological picture is identical with the hyperplasia of Graves' disease. On the other hand, in from only 50 to 75 per cent of cases of Graves' disease is the thyroid hyperplastic. Crile, therefore, concludes that hyperplasia of the thyroid cannot be the cause of Graves' disease any more than it is the cause of pregnancy or of tuberculosis or of adolescence—it is an end effect, not a cause. But resection of thyroid tissue does mitigate or cure Graves' disease, whereas such a procedure would not end pregnancy, cure infection or assist adolescence. The cases of Graves' disease which were not entirely cured or which partially relapsed after resection did so for the following reasons. (a) Psychic drive—"The more intense the struggle of man against man, the more difficult it is to cure Graves' disease

completely." Crile points out that the disease is rarely found in the degenerate, in idiots or in moral defectives. Sudden emotional or physical shock, great worry or strain, etc., will cause relapse. (b) Acute infections are also a cause. (c) Intestinal auto-intoxication will prolong the disease. (d) Pregnancy may cause it; with its termination the relapse subsides. (e) Adolescence is another cause and one which cannot be controlled. The interesting conclusion follows that the thyroid changes are end effects and not the cause of Graves' disease, but that resection of the thyroid breaks "a link in the kinetic chain," and that maximal improvement demands a combination of surgical and medical measures.—H. L.

(THYROID) Malignant goitre. Crotti (A.), Ohio M. J. (Columbus), 1917, **13**, 807-809.

Malignant goitre develops in an already existing goitre in 90 per cent of the cases; a malignant tumor developing in a normal thyroid is rare; the tumor is nearly always of connective tissue origin, as sarcoma, etc.; malignant degeneration of goitre occurs mostly between 40 to 60 years of age. Sarcoma occurs mostly in young people, cancer in old. Malignant goitre is more common in women, and most frequent at the menopause. It may develop very acutely and is then difficult to differentiate from acute woody thyroiditis. It may be latent and the gland may hardly be modified in appearance, but numerous metastases may occur in lungs and bones. The thyroid origin is usually discovered at autopsy; this type is rare. Usually malignant goitre is subacute, and develops from a goitre which has been stationary for years. Crotti gives an excellent clinical picture of the symptoms and physical signs present in these cases, all of which is so detailed that it cannot be abstracted. Cancer metastases in bones are most frequently due to thyroid cancer; a prostatic origin comes second. The skull is the most common site for thyroid cancer metastasis, then the pelvis, sternum, femur, clavicle, lower jaw and shoulder blades. Malignant goitre does not necessarily produce hyper- or hypo-thyroidism. Interference with respiration and deglutition, in a patient with a goitre which has becomes irregular and peculiarly hard, accompanied by shooting pains, strongly suggests the presence of malignant goitre. Crotti insists that the only therapy deserving consideration is surgery, and that if the high mortality is to be reduced, it rests with the family physician to diagnose cases sufficiently early before the neoplasm has burst through the capsule. "An alarming pessimism" is the best state of mind for the general physician, so that he may suspect malignancy early.—H. L.

(THYROID) Acute febrile epidemic myxedema (Mixedema acuto febbrile epidemico). Ditelli (S.), Gazz. d. Osp. (Milano), 1920, **41**, 696.

A short note. A mild epidemic of myxedema, beginning with a swelling of the head, the neck and the thorax was observed in Nicosia, Italy. The patients became normal again after a few weeks without any treatment.—J. K.

(THYROID) Case of severe hemorrhage in a cystic goiter with danger of suffocation (Su di un caso di grave emorragia in gozzo cistico con imminente pericolo di soffocazione). Dossena (G.), Morgagni (Milano), 1920, **62**, 291-296.

Report of a case caused by strumectomy. Two good illustrations.—J. K.

(THYROID) Direct muscular protection to the goiter residue in primary closing of the wound after strumectomy without drainage (Die direkte Muskeldeckung des Kropfrestes beim primären Wundschlusz nach Strumektomie ohne Drainage). Dubs (J.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1294-1296.

Of technical surgical interest.—J. K.

(THYROID) Surgical goitre. Else (J. E.), Northwest Med. (Seattle), 1917, **17**, 16-20.

The author considers the indications for operation upon the thyroid to be: (1) cosmetic, (2) mechanical, (3) toxic, (4) malignancy. Only the second and third are considered in this paper. The mechanical indications are all due to pressure, either upon the trachea, esophagus, nerves or adjacent blood vessels. Pressure upon the trachea may result in deflection, lateral compression, cough, interference with expiration producing emphysema, edema of the mucosa and, rarely, complete occlusion with death. Else refers to the various types of intrathoracic goitre which may cause compression. He then mentions the varieties of toxic goitre—exophthalmic or hyperplastic, and toxic or cardiovascular, which in turn are due to adenoma, adenomatosis, and regeneration or compensatory hyperplasia. Attention is called to the lack of correlation between the clinical findings and pathological changes. Depending upon the quantity of colloid present Else speaks of foetal, adult and mixed adenoma. One cannot tell from the microscopic appearance whether toxic symptoms were present or not. Eye signs are absent in adenomas. The author follows closely the classification and ideas of Wilson and Plummer. Preliminary ligation of the superior thyroid artery is urged in severe toxic cases, to be followed shortly by lobectomy.—H. L.

(THYROID) The heart in 17 cases of Graves' disease and 7 cases of goiter (Herzuntersuchungen an 17 Fällen von Morbus Basedow und 17 Fällen von Struma). Fähr, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1178.

Data reported elsewhere.—J. K.

(THYROID) Abnormal goat milk. Grimmer (W.), Milch. Zentralbl., 1920, **49**, 67-69; Physiol. Abst., **5**, 427.

Milk from thyroidectomized goats was found over a considerable period of time to be abnormal. Such milk has a relatively high specific gravity, low caseinogen and sugar content and a notable increase in the weight of the non-fat solids. Calculations based on the Fleischmann and Babcock formula yielded high values, not in harmony with the analytical results.—R. G. H.

(THYROID) Basedow und THYMUS. Haberer. Mitt. a.d. Grenzgeb. Med. u. Chir. (Jena), 1920, **32**, 329-353.

In cases of Graves' disease or simple goitre, treated surgically, it is often not enough to reduce the thyroid, but it is necessary, when possible, to reduce the thymus also. This is not a proof that there is a thymic factor in Graves' disease. It is very doubtful whether this exists. Haberer treated 35 cases with reduction of both thyroid and thymus. Three patients died. One of them was a woman with a very weak heart who was in the last months of pregnancy. The two others showed nervous tension after the operation; the pulse was too rapid to be counted; there was fever and cyanosis. In both cases it was found at autopsy that a large part of the thymus had been left in the body. In most other cases after the operation nervousness disappeared at once and the pulse became regular and quiet, although in two the heart symptoms and the nervousness persisted for some time. In both cases a relatively large part of the thymus had been left. One patient was at the point of death on admission to the hospital. He had repeatedly undergone strumectomy without success. After strumectomy and thymectomy complete recovery occurred. In 10 patients the goitre returned, but the other symptoms of Graves' disease never came back. If thymectomy is not performed but only a part of the thyroid removed, Graves' disease often shows real recurrences. Some cases are still healthy seven years after operation.—J. K.

(THYROID) War diet and hypothyroidism (Kriegsernährung und Hypothyroidismus). Hinz (C.), Med. Klin. (Berlin), 1920, **16**, 313-315.

Hinz, of the University Medical Polyclinic, at Rostock, quotes cases to show that there is a close relationship between hypothyroidism and war edema. He alludes to the success obtained by administration of thyroid extract in many cases of war edema, and mentions the autopsy findings of Oberndorfer, who found marked atrophy of the thyroid. He also alludes to Adler's experiments on hibernating animals as illustrating the connection between diminution of food metabolism and the function of the thyroid. By injecting hibernating animals in which respiratory movements and temperature are reduced to a minimum, Adler succeeded in waking them after one to three hours, and raising their temperature from 8 degrees

C. to 35 degrees C. Hinz suggests that in war edema the insufficiently nourished organism endeavors in like manner to protect itself by a diminution of thyroid function.—Med. Sc. Abst. & Rev., **3**, 215.

(THYROID) A new pair of scissors for operating for goitre (Ein neue Kropfschere). Hofmann (A.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1257.

A new surgical instrument.—J. K.

(THYROID) Myxedema. Kaspar, München. med. Wchnschr., 1920, **67**, 1190.

A typical case in an infant of three months.—J. K.

(THYROID) Demonstration of four cases of cretinism (Demonstration von 4 Fällen von Kretinismus). Kellner, Deutsche med. Wchnschr., 1920, **46**, 1130.

After the demonstration the author discusses the mortality of mentally deficient children. This is always much higher than in normal persons, but during the war the ratio was increased. The bad hygienic conditions in Germany, the increased number of alcoholics and patients suffering with syphilis are the causes of the rapid increase in the number of mongoloids, myxedemas, and cretins.—J. K.

Ligation of the THYROID arteries in operation for goiter (Zur Frage der Unterbindung sämtlicher Schilddrüsenarterien bei Kropfoperation). Kreuter (E.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1317-1318. Lobenhoffer, Ibid., 1319-1322.

Of technical surgical interest.—J. K.

(THYROID) Goiter (Struma). Linhart, Wien. klin. Wchnschr., 1920, **33**, 763.

A short note on a very large retrosternal goiter and the way in which it was removed.—J. K.

(THYROID) Mistakes in one hundred thyroidectomies; with description of a new method of thyroid cauterization in treating exophthalmic goiter. Mason (J. Tate), J. Am. M. Ass., (Chicago) 1920, **75**, 160-162.

A report of a series of 100 thyroidectomies covering a period of eight years. Fifty-eight patients were operated upon for toxic adenomas; one patient died. Forty-two patients were operated upon for exophthalmic goiter and five died. The symptomatology of the two types of cases is briefly discussed. The one death in the first series was due to refusal of the patient to undergo preliminary rest treatment. Mason feels that the most serious mistakes are due to lack of a full appreciation of the dangers of the crisis in exophthalmic

goiter, and to attempting too much in extremely bad cases. As to technic, local anesthesia is begun by pressure for 30 seconds with a cotton applicator frozen with ethyl chloride, upon the point chosen for the first needle puncture. Procain is then infiltrated as usual, the goiter exposed, and small portions cauterized. This is repeated every two or three days until the patient is considered a safe risk for ligation or thyroidectomy. This fractional cauterization may replace ligation in time.—F. S. H.

(THYROID) Mongoloid idiocy. Meltzer, Berl. klin. Wchnschr., 1920, **57**, 791-792.

Although the thyroid is frequently asserted to be at fault in mongoloid idiocy, this is certainly not true in all cases. Post-mortem examinaitons often do not show that changes have taken place in the thyroid and often iodine has no effect upon the disease.—J. K.

(THYROID) A case of myxedema after operation for Graves' disease (Ein Fall von Myxödem nach operiertem Morbus Basedow). Munk, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1154.

Previously abstracted from the München. med. Wchnschr.—J. K.

The treatment of THYROID toxicosis with iodine (Ueber Jodbehandlung bei Thyreotoxicose). Neisser (E.), Berl. klin. Wchnschr., 1920, **57**, 461-463.

Most authorities consider the administration of iodine as extremely dangerous in cases of Graves' disease. Neisser has seen cases in which iodine cured the patient almost at once. One of his patients was a man of 45, who had a simple goiter. After x-ray treatment the goiter became smaller, but symptoms of Graves' disease (tachycardia), great loss of weight, diarrhoea, perspiration, and exophthalmus developed. Potassium iodide in small doses (three times daily, 10 drops of a solution of 1:20) cured the patient in a very short time. Six other cases are described, one a young woman in whom Graves' disease followed **ovariotomy.** In this case, also, the iodine treatment was successful. The author points out how we may distinguish the cases to be treated with iodine. According to him, there are four classes of patients in whom iodine treatment is advisable; those in whom the loss of weight has reached the maximum and whose weight is therefore stationary; those with small or diminishing goiters; those without exophthalmus; and those with tachycardia but without dilation of the heart. For these cases the author recommends the use of a solution of sodium or potassium iodide, 1:20, beginning with 2 to 5 drops three times daily, and increasing gradually to 20 drops three times daily.—J. K.

(THYROID) Goitre exophthalmique et syphilis. Pfeiffer (C.), Progres méd. (Paris), 1920, 3.s., **35**, 187-188.

Pfeiffer, of Dijon, records three cases of acute Graves' disease in which the causal emotion, which was insufficient in itself to produce a permanent anatomical change, was accompanied by an important factor, viz., active syphilitic infection. As these three cases were the only examples of so-called exophthalmic goiter which he had met with during eighteen months' observation of several hundred cases of commotion, Pfeiffer is convinced that every case of exophthalmic goiter of so-called emotional origin, occurs on a syphilitic soil.—Med. Sc. Abst. & Rev., **3**, 213.

(THYROID THYMUS) Syndrome polyglandulaire thymothyroïdien avec hydrocéphalie. Sabrazès (J.) & Dupérié (R.), Gaz. hebd. d. sc. méd. de Bordeaux, 1920, **41**, 350-351; 410-415.

The authors report the case of a woman, aged 29, the daughter of a goitrous mother and alcoholic father, who, in addition to hydrocephalus, presented a congenital thyro-ovarian insufficiency which was improved by opotherapy. But a deep goiter and a large thymus were refractory to treatment and contributed to a fatal termination of an attack of typhoid. Examination of the glands of internal secretion at autopsy showed normal parathyroid tissue and a hypophysis which was in a state of excessive activity. Sclerotic changes in the choroid plexus and various ependymal changes appear to have played an important part in the mechanism of the hydrocephalus.—Med. Sc. Abst. & Rev., **3**, 220.

The relation of THYROID secretion to the condition of the skin—and incidentally to old age. Starr (M. A.), Constrib. Med. & Biol. Research. . . . Sir W. Osler, N. Y., 1919, **2**, 1184-1185.

Starr has found that the dryness of the skin, brittleness of the nails, and the loss of hair usually met with in old age may be stopped by taking small amounts of thyroid (not more than 1 grain of the Burroughs and Welcome extract in divided doses in a day). The patients feel more active mentally and physically, and suffer less from depression and insomnia. Starr concludes that some of the conditions supposed to be due to old age are actually due to a diminution in the activity of the thyroid gland and consequently may be obviated or removed by the constant use of thyroid extract as age advances.—Med. Sc. Abst. & Rev., **3**, 216.